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Original Article

Predictors of in-hospital mortality for sepsis patients in intensive care units

Kun Chen[1], Chengwei Gao[2], Qiuxiang Zhou[1], Wenfang Li[1], Zhaofen Lin[1]

[1]Department of Emergency, Changzheng Hospital, The Second Military Medical Univercity, Shanghai 200003, China; [2]Intensive Care Unit, The People's Hospital of Gucheng, Hubei, 441700, China

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Abstract: Sepsis is a major cause of death in patients in intensive care units. A better understanding of associations between patients' characteristics and in-hospital mortality for sepsis patients in intensive care units will help improve their outcomes. This study aims at investigating the predictors of in-hospital mortality for sepsis patients in intensive care units based on patients' characteristics and clinical evaluations. A single-center, retrospective study was performed based on data collected from patients in intensive care units of our affiliation hospital, from January 2010 to April 2014. General characteristics, respiratory function, blood routine examinations, liver and kidney functions, coagulation function, blood culture, C-reactive protein, procalcitonin, APACHE II score and SOFA score were recorded. The multiple logistic regression analysis was performed to analyze independent risk factors for in-hospital mortality and ROC curves were created. A total of 134 patients were enrolled and were further divided as non-survival group (n=38) and survival group (n=96). Decreased APACHE II score, total bilirubin, and platelet count were independently associated with in-hospital mortality for sepsis patients in intensive care units. The APACHE II score offered sensitive and specific predictive values, and platelet count and total bilirubin levels had some reference values for in-hospital mortality for sepsis patients in intensive care units. In conclusion, this study has demonstrated that APACHE II score could offer sensitive and specific predictive values for in-hospital mortality for sepsis patients in intensive care units.

Keywords: Sepsis, in-hospital mortality, predictors, intensive care units

Introduction

Sepsis, a systemic inflammatory response caused by infection, is a serious damage and life threatening syndrome for individuals [1-3]. As one of the major diagnoses among hospitalized patients, sepsis accounts for 2.15% of all hospitalizations in the United States and the situation is also similar in Europe [1, 4, 5]. In intensive care units, sepsis is also a common encountered syndrome and its incidence is approximately 11-15% [1, 4, 5]. The annual cost due to sepsis increases by 57% in the past 5 years and reaches more than $24 billion in the United States. Due to the increasing of ageing population, antimicrobial resistance, more accessible medical technology and interventions, and immunosuppressive therapies, the incidence of sepsis will continue to increase both in the developing and the developed countries [6-9].

Despite great advances have been achieved in supportive intensive care and development of advanced appropriate antibiotics, sepsis remains the major cause of death in patients in intensive care units [10, 11]. The overall mortality rate of sepsis has been estimated to be varied between 30% and 50% in different studies [6, 10, 12]. Early identification and treatment of sepsis with high risk of mortality has already been shown to significantly improve survival [3, 11, 13]. As long as the early goal-directed therapy is initiated, the mortality rate could be decreased as much as 16% [3, 11, 13]. Any delay might prevent prompt initiation of treatment in a condition that is amenable to improved outcomes with early interventions in sepsis patients [8, 14, 15]. Therefore, the ability to quickly and accurately evaluate the disease severity and mortality risk in sepsis patients is extremely important.

Table 1. General characteristics of patients in the non-survival group and the survival group

General Characteristics	Non-survival (n=38)	Survival (n=96)	*P* value
Age	59.47±2.376	51.48±1.811	0.015
No. (%) male	26 (68%)	69 (72%)	0.692
Height (cm)	169.24±1.158	170.92±0.693	0.205
Weight (kg)	65.21±1.672	66.18±0.875	0.580
Total hospitalization time	22.82±3.802	32.86±2.933	0.057
Hospitalization time in ICU	18.39±2.793	27.59±2.931	0.067
No. (%) blood culture positive	15 (39%)	27 (28%)	0.202
APACHE-II score	22.39±0.883	12.19±0.558	< 0.001
SOFA score	10.5±0.496	7.3±0.341	< 0.001
Infection source			0.410
Lung	11 (28.9%)	38 (39.6%)	
Urinary system	2 (5.3%)	8 (8.3%)	
Blood	15 (39.5%)	27 (28.1%)	
Skin and soft tissue	0 (0%)	5 (5.2%)	
Chest	2 (5.3%)	4 (4.2%)	
Abdomen	8 (21.1%)	14 (14.6%)	
Severe trauma	15 (39.5%)	36 (37.5%)	0.832

APACHE-II score: Acute Physiology and Chronic Health Evaluation II Score SOFA score: Sequential Organ Failure Assessment Score.

The risk factors of in-hospital mortality for sepsis patients in intensive care units are multifactorial [10, 13, 16-18]. Several studies have demonstrated that patients' characteristics including comorbid conditions and race would affect mortality [10, 13, 19-21]. However, data are still relative limited regarding patients' characteristics and clinical evaluations as potential confounders in in-hospital mortality for sepsis patients in intensive care units [10]. A better understanding of potential associations between patients' characteristics and in-hospital mortality for sepsis patients in intensive care units will definitely greatly help policy makers and healthcare administrators improve sepsis patients' clinical outcomes [10].

In the present study, we aim at investigating the predictors of in-hospital mortality for sepsis patients in intensive care units based on patients' characteristics and clinical evaluations.

Methods study population

This study was a single-center, retrospective study performed based on data collected from patients in intensive care units of our affiliation hospital, from January 2010 to April 2014. The study was approved by our Institutional Review Board and informed consent and authorization was waived as patient data used in the present study were obtained from existing medical records.

Sepsis is defined as the presence of infection and also systemic manifestations of infection. In detail, the diagnostic criteria of sepsis include body temperature > 38°C, or < 36°C, heart Rate > 90 bpm, respiratory rate > 20 bpm, $PaCO_2$ < 32 mmHg, WBC > 12,000/mm^3, < 4,000/mm^3, or > 10% bands, and suspected or present source of infection. The exclusion criteria were pregnancy, human immunodeficiency virus (HIV) infection, underlying major disease other than sepsis, chemotherapy or radiation therapy within 4 weeks before the study, cardiopulmonary resuscitation within 72 hours before study commencement. Based on the inclusion and exclusion criteria as documented above, a total of 134 patients were enrolled in this study.

Data collection and outcome measures

Data collection was performed from the electronic medical record using a data abstraction form by two independent investigators. A third investigator randomly selected 15% of the data abstraction forms submitted by each investigators and confirmed the consistency and accuracy of the data collected by these two independent investigators.

For all enrolled patients, the following clinic variables were recorded: (1) general characteristics including age, gender, height, weight and hospitalization time; (2) respiratory function including arterial partial pressure of oxygen (PaO_2), oxygenation index, partial pressure of carbon dioxide in artery ($PaCO_2$), lactic acid and base excess; (3) blood routine examinations including white blood cells (WBC), platelet (PLT), and hemoglobin; (4) liver and kidney functions including total bilirubin, alanine aminotransferase (ALT), aspartate transaminase (AST), serum creatinine, blood urea nitrogen and albumin; (5) coagulation function including prothrombin ti-

Table 2. Clinic Evaluations of patients in the non-survival group and the survival group

Clinic Evaluations	Non-survival (n=38)	Survival (n=96)	*P* value
Oxygenation index	176.97±12.324	206.86±8.163	0.050
PaO_2 (mmHg)	87.16±5.457	93.27±3.415	0.343
$PaCO_2$ (mmHg)	35.26±1.742	35.67±1.119	0.846
Lactic acid (mmol/L)	3.195±0.4606	1.851±0.169	0.001
Base excess (mmol/L)	-4.929±1.2715	-2.622±0.4631	0.001
WBC (×10^9/L)	14.545±1.9214	12.558±0.7974	0.258
PLT (×10^9/L)	136.97±14.637	195.92±10.745	0.003
Hemoglobin (g/L)	93.84±3.14	104.99±2.35	0.009
CRP (mg/L)	93.5282±12.52222	75.1283±6.70377	0.167
Total bilirubin (umol/L)	88.26±21.509	28.08±4.209	< 0.001
ALT (U/L)	196.16±98.045	115.89±25.429	0.277
AST (U/L)	198.5±83.193	124.94±27.513	0.282
Serum creatinine (umol/L)	156.82±29.882	94.33±13.288	0.029
Blood urea nitrogen (mmol/L)	14.7±1.6361	11.015±1.728	0.212
Albumin (g/L)	27.184±1.0161	31.781±0.6375	< 0.001
PCT (ng/mL)	10.9766±2.9587	4.3368±0.48228	0.001
PT (S)	17.13±1.033	14.14±0.399	0.001
APTT (S)	43.68±2.768	34.01±1.187	< 0.001
D-dimer (ug/L)	4815.79±526.89	4399.54±325.269	0.499
Plasma fibrinogen (g/L)	3.1353±0.44511	3.5818±0.1855	0.273

PaO_2: Arterial partial pressure of oxygen; $PaCO_2$: Arterial partial pressure of carbon dioxide; WBC: White blood cell; PLT: Platelet; PT: Prothrombin time; CRP: C-reactive protein; ALT: Alanine aminotransferase; AST: Aspartate transaminase; PCT: Procalcitonin; APTT: Activated partial thromboplastin time.

me (PT), activated partial thromboplastin time (APTT), D-dimer and plasma fibrinogen; (6) blood culture, C-reactive protein (CRP) and procalcitonin (PCT); (7) APACHE II score and SOFA score. APACHE II score was calculated based upon initial values of 12 routine physiologic measurements, age, and previous health status as previous described [22, 23]. SOFA score was also calculated as described previously [22, 23].

The primary outcome in this study was all-cause mortality, defined as occurring within the hospital.

Statistical analysis

The continuous data were presented as mean ± SEM, and the Student t-test was used to compare the means between Non-survival group and Survival group. Categorical variables presented as frequency distributions, and the chi-square was used to compare the difference between groups. Nonparametric data was analyzed using the Mann-Whitney U test. Multivariable logistic regression was then performed to identify independent risk factors for patients mortality after these univariate analyses. Risk factors whose significance was less than 0.05 obtained in univariate analysis were enrolled in the model. ROC curves were displayed as the true-positive rate (TPR) versus the false-positive rate (FPR). The area under the ROC curve (AUC), a measure of discrimination accuracy, was reported.

Results

General characteristics

During the study period, 134 patients that met the inclusion criteria were enrolled in the present study. According to the in-hospital mortality, these 134 patients were further divided as non-survival group (n=38) and survival group (n=96), respectively.

The general characteristics of the non-survival group and survival group were indicated in **Table 1**. No significant difference was observed in sex, height, weight, total hospitalization time, hospitalization time in intensive care units, blood infection culture positive rate, infection source, and severe trauma between these two groups. However, the non-survival group was older and had a higher APACHE-II score and SOFA score.

Clinic evaluation

The clinic evaluation of these two groups was shown in **Table 2**. There were no significant difference between two groups in oxygenation index, arterial partial pressure of oxygen, arterial partial pressure of carbon dioxide, white blood cell count, C-reactive protein, alanine aminotransferase, aspartate transaminase, blood urea nitrogen, D-dimer, and plasma fibrinogen. However, the non-survival group had a higher

Table 3. Multivariable analysis of independent risk factors for in-hospital mortality

	Adjusted odds ratio	95% CI	*P* value
Decreased APACHE II score	0.736	0.659, 0.823	< 0.001
Decreased level of total bilirubin	0.989	0.980, 0.997	0.006
Decreased platelet count	1.007	1.000, 1.013	0.036

The dependent variable is mortality. The independent variables include all variables in **Tables 1** and **2** with *P* values less than 0.05. beta value=0.10.

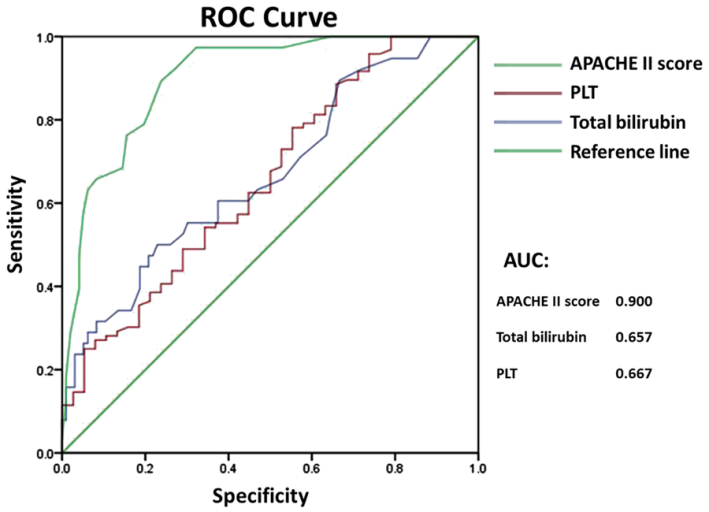

Figure 1. ROC curves constructed to compare the relative concentrations of APACHE II score, platelet count, and total bilirubin. The AUC of APACHE II score is 0.900 (P < 0.001, 95% CI=0.848~0.953), of platelet count is 0.657 (P=0.005, 95% CI=0.553~0.760), of total bilirubin is 0.667 (P=0.003, 95% CI=0.565~0.770).

Table 4. The parameters of ROC curves

Variables	AUC	*P* value	95% Confidence Interval	
			Lower Bound	Upper Bound
PLT (×10^9/L)	0.657	0.005	0.76	0.553
APACHEII	0.900	0.001	0.848	0.953
Total bilirubin	0.667	0.003	0.565	0.77

lactic acid, total bilirubin, serum creatinine, procalcitonin, as well as longer prothrombin time, and activated partial thromboplastin time. In addition, the non-survival group also had a lower base excess, platelet count, hemoglobin and albumin.

Multiple logistic regression analysis

The multiple logistic regression analysis was further performed to analyze independent risk factors for in-hospital mortality for sepsis patients in intensive care units. The dependent variable is mortality. The independent variables include all variables in **Tables 1** and **2** with *P* values less than 0.05 were adjusted in **Table 3**. Decreased APACHE II score, total bilirubin, and platelet count were independently associated with in-hospital mortality for sepsis patients in intensive care units (**Table 3**).

Receiver operating characteristic (ROC) curves analysis

As shown in **Figure 1**, ROC curves of decreased APACHE II score, total bilirubin, and platelet count were constructed and the area under the curves (AUC) were identified to be 0.900, 0.657, and 0.667, respectively (**Table 4**). Our results demonstrate that the APACHE II score offers sensitive and specific predictive values, and platelet count and total bilirubin levels have some reference values for in-hospital mortality for sepsis patients in intensive care units.

Discussion

The major findings of the present study are as follows. Firstly, the non-survival group is older and has a higher APACHE-II score and SOFA score. Secondly, the non-survival group has a higher lactic acid, total bilirubin, serum creatinine, procalcitonin, as well as longer prothrombin time, and activated partial thromboplastin time. Thirdly, the non-survival group has a lower base excess, platelet count, hemoglobin and albumin. Fourthly, decreased APACHE II score, total bilirubin, and platelet count are independently associated with in-hospital mortality for sepsis patients in intensive care units. Finally, the APACHE II score offers sensitive and specific predctive values, and platelet count and total bilirubin levels have some reference values for in-hospital mortality for sepsis patients in intensive care units.

Sepsis remains the major cause for the admission to ICU, contributing to nearly 25% patients

in ICU [11, 15]. Despite the medical advance, the mortality is still extremely high and early start of proper therapy for patients at high risk of in-hospital death will help decrease that [1]. Therefore, it is highly needed to identify those patients are most likely to encounter in-hospital death. Here we provided direct evidence that APACHE II score can offer sensitive and specific predctive values for in-hospital death, indicating that APACHE II score is useful for identifying those patients at high risk of in-hospital death.

Actually APACHE II score has been used to determine if a patient is eligibility for some therapies [11, 20]. Patients having an APACHE II score over 25 have been recommended to receive activated protein C (APC) therapy [11, 20]. SOFA score has been reported to have moderate predict values for in-hospital mortality for sepsis patients [11], however, here though we found that SOFA score was higher in the non-survival group, it can not predict in-hospital mortality for sepsis patients in intensive care units in our cohort. This could be caused by race difference.

Several limitations of this study should be highlighted. First, death due to sepsis mostly occurs at 30 days or later, however, here we used in-hospital mortality as a endpoint. Secondly, the number of patients is relatively small. Finally, this is an observational study and it is highly needed to conduct an intervention study to determine if treatment under the instruction of APACHE II score could reduce the in-hospital mortality for sepsis patients in intensive care units.

In conclusion, this study has demonstrated that APACHE II score could offer sensitive and specific predctive values for in-hospital mortality for sepsis patients in intensive care units.

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Disclosure of conflict of interest

None.

Address correspondence to: Drs. Wenfang Li and Zhaofen Lin, Department of Emergency, Changzheng Hospital, The Second Military Medical Univercity, NO. 415 Fengyang Road, Shanghai 200003, China. Tel: 0086-21-81886271; Fax: 0086-21-63520020; E-mail: WenfangLi_sh@163.com (WFL); ZhaofenLin_sh@163.com (ZFL)

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