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Analysis of risk factors for death in patients with sepsis

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Abstract: Objective To construct a death risk prediction model of sepsis, in order to provide reference for improving the early warning of death risk and improving the outcome of sepsis patients. **Methods** The data of sepsis patients who met the diagnostic criteria of *Sepsis-3.0* in the comprehensive ICU of Tongji Hospital Affiliated to Tongji Medical College of Huazhong University of Science and Technology from January 2019 to May 2022 were retrospectively collected. The *t* test, chi-square test and nonparametric Mann-Whitney *U* test were used to conduct univariate analysis on the death risk of sepsis patients, and then multivariate analysis was carried out, and a prediction model of sepsis death risk was established. **Results** The survival status of 28 days after admission to ICU was calculated. Of 286 patients with sepsis, 165 (57.69%) survived and 121 (42.31%) died. The initial infection sites were lung, abdominal, skin and soft tissue, urinary tract. The time between diagnosis of sepsis and admission, time of onset of first cluster therapy, age, lactic acid level and APACHE Ⅱ score at admission to ICU, occurrence of hypothermia, continuous renal replacement therapy (CRRT), first symptoms of fever at onset, length of stay in ICU, the levels of creatinine, procalcitonin and fibrinogen at ICU admission were independent influencing factors of death in sepsis patients (P<0.05). The area under the ROC curve of the mortality risk prediction model for sepsis patients was 0.970, with a sensitivity of 0.893, a specificity of 0.933, and a maximum Jordan index of 0.826. **Conclusion** The prevention focus of death risk in sepsis patients needs to be moved forward, the risk factors of pre-hospital death of patients should be paid attention to, the changes in the condition before confirmatory treatment should be grasped, in order to reduce and avoid adverse outcomes. In addition, the preliminarily constructed mortality risk prediction model for sepsis patients in this study has good predictive ability, and can provide certain reference value in clinical work.

Keywords: Sepsis; Death; Risk factors; Protective factors; Risk prediction model
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Sepsis is a relatively common clinical condition characterized by a systemic inflammatory response, which, as the disease progresses, can lead to organ dysfunction, shock, and high mortality. Globally, there are approximately 48.9 million new cases of sepsis annually, with around 11 million deaths. In China, the mortality rate for sepsis is about 33.6%. Sepsis remains a major global health threat and is one of the significant disease burdens in China, severely impacting public health and being closely linked to socioeconomic development.

Currently, research on factors affecting sepsis-related mortality is extensive and covers a broad range of topics, but it tends to focus on specific populations (such as the elderly and neonates) or certain diseases (such as urosepsis related to urinary stones), and is more often based on in-hospital data. However, data obtained before diagnostic treatment, which is closely related to patient management, may influence the patient's prognosis. Therefore, this study aims to include adult sepsis patients in the comprehensive ICU, using pre-hospital indicators, diagnostic, and treatment-related data to develop a death risk prediction model, in order to provide a basis for improving sepsis mortality risk alerts, developing prognosis management strategies for sepsis patients, and improving patient outcomes.

1 Materials and Methods

1.1 Clinical Data

A convenience sampling method was used to select sepsis patients admitted to the comprehensive ICU of Tongji Hospital, affiliated with Huazhong University of Science and Technology, between January 1st, 2019, and May 31st, 2022. This study was approved by the Medical Ethics Committee of Tongji Hospital (TJ-IRB20220711).

Inclusion criteria: (1) Meet the *Sepsis-3.0* diagnostic criteria for sepsis; (2) Age ≥ 18 years.

Exclusion criteria: (1) Missing or duplicate medical records; (2) Diagnosed with COVID-19. A total of 286 patients were included in the final analysis.

1.2 Methods

All sepsis patients admitted to the ICU were immediately monitored for vital signs and had blood samples collected. Additional patient data collected included general information (gender, age, residence, smoking and drinking history, initial infection site, underlying diseases), pre-hospital conditions, treatment history (referral status, initial symptoms, time from onset

to first visit, time from onset to ICU admission, time from sepsis diagnosis to ICU admission, and pre-ICU bundle therapy), vital signs at ICU admission [temperature, heart rate, respiration rate, systolic blood pressure, mean arterial pressure (MAP)] and laboratory indicators [platelet count, hemoglobin, white blood cells, albumin, activated partial thromboplastin time (APTT), prothrombin time, fibrinogen, serum procalcitonin (PCT), C-reactive protein (CRP), B-type natriuretic peptide (BNP), high-sensitivity troponin I (hs-TnI), D-dimer, interleukin (IL)-6, lactate, blood glucose, total bilirubin, urea, creatinine] were recorded. The Acute Physiology and Chronic Health Evaluation II (APACHE II) score and average urine output within 24 hours of ICU admission, bacterial culture results (blood, urine, sputum, and drainage cultures), incidence of hypothermia (axillary temperature<36°C), and treatment interventions [including continuous renal replacement therapy (CRRT), mechanical ventilation, vasopressor use, 24-hour intake/output, length of ICU stay] were also documented.

1.3 Statistical Methods

The collected data were analyzed using SPSS 22.0 software. Normally distributed continuous data were presented as $\overline{X} \pm s$ and compared using the independent two-sample t-test. Non-normally distributed data were expressed as $M(P_{25}, P_{75})$, and Mann-Whitney U test was used to compare the difference between two groups. Categorical data were expressed as percentages or proportions and compared using the chi-square test. Variables that showed statistical significance in univariate analysis were included in logistic regression analysis to identify prognostic risk and protective factors for sepsis mortality. A death risk prediction model was constructed, and the receiver operating characteristic (ROC) curve was plotted to calculate the area under the curve (AUC), sensitivity, and specificity. $P<0.05$ was considered that the difference was statistically significant.

2 Results

2.1 Univariate Analysis of Factors Associated with Sepsis Mortality

Among the 286 patients, 121 died, with a 28-day mortality rate of 42.31% after ICU admission. There were statistically significant differences between the survival group and the death group in terms of age, place of residence, underlying diseases such as tumors or heart disease, initial infection site in the lungs or abdominal cavity, initial symptoms such as fever, consciousness disorders or respiratory symptoms, referral, and time from first visit to onset>6 hours, time from ICU admission to onset>72 hours, time from diagnosis of sepsis to onset>24 hours, time from diagnosis of sepsis to hospital admission>1 hour, time from first bundle treatment to onset>6 hours, Gram-positive bacteria detection rate, heart rate, incidence of hypothermia, urine output and fluid balance within 24 hours of ICU admission, lactate, albumin, hs-TnI, IL-6, PT, APACHE II score, ventilator use rate, duration of ventilator use, CRRT rate, and vasopressor use rate **[Tab.1 to Tab.4].**

Tab. 1 Univariate analysis of mortality factors in patients with sepsis (general data) [case (%)]

Indicators	Survive (n=165)	Death (n=121)	Z/χ^2 value	P value
Age (years) [a]	57.00 (49.00, 65.00)	63.00 (54.00, 73.00)	3.474	0.001
Gender				
Male	84(50.91)	64(52.89)	0.110	0.740
Female	81(49.09)	57(47.11)		
Residence area				
City	74(44.85)	75(61.98)	8.220	0.016
Township	29(17.58)	15(12.40)		
Countryside	62(37.57)	31(25.62)		
Smoking history	45(27.27)	23(19.01)	2.631	0.105
Drinking history	27(16.36)	18(14.88)	0.117	0.733
Basic diseases				
Respiratory Disease	9(5.45)	14(11.57)	3.531	0.060
Hypertension	53(32.12)	38(31.40)	0.017	0.898
Liver and kidney diseases	50(30.30)	37(30.58)	0.003	0.960
Diabetes	36(21.82)	23(19.01)	0.337	0.562
Tumour	26(15.76)	32(26.45)	4.933	0.026
Heart Disease	14(8.48)	22(18.18)	5.966	0.015

Note: [a] meant the data was represent in the form of $M(P_{25}, P_{75})$.

Tab. 2 Univariate analysis of mortality factors in patients with sepsis (initial infection site and first symptoms) [case (%)]

Indicators	Survive (n=165)	Death (n=121)	χ^2 value	P value
Infection site				
Lungs	42(25.45)	50(41.32)	8.055	0.005
Urinary system	35(21.21)	5(4.13)	16.928	<0.001
Skin and soft tissue	11(6.67)	15(12.40)	2.773	0.096
Gastrointestinal tract	16(9.70)	4(3.31)	4.384	0.036
Blood flow	6(3.64)	1(0.83)		0.245
Intracranial	1(0.61)	1(0.83)		1.000
Initial symptoms				
Fever	80(48.48)	25(20.66)	23.259	<0.001
Abdominal and digestive system symptoms	55(33.33)	46(38.02)	0.670	0.413
Non-abdominal pain	30(18.18)	24(19.83)	0.125	0.724
Consciousness disorders	5(3.03)	18(14.88)	13.246	<0.001
Respiratory symptoms	16(9.70)	26(21.49)	7.746	0.005

2.2 Logistic Regression Analysis of Factors Associated with Sepsis Mortality

Sepsis mortality was treated as the dependent variable. The significant factors from the univariate analysis and clinically relevant variables were selected as independent variables for multivariate logistic regression analysis. The coding system was as follows:

1.First symptoms without fever=0, with fever=1;
2.Initial infection was lungs: no=0, yes=1;
3.Initial infection was abdominal cavity: no=0, yes=1;
4.Initial infection was skin and soft tissue: no=0, yes=1;
5.Initial infection was urinary system: no=0, yes=1;
6.No hypothermia =0, hypothermia=1;
7.No CRRT treatment=0, CRRT treatment=1;
8.Time from diagnosis of sepsis to hospital admission ≤ 1 hour=0,>1 hour=1;
9.Time from first bundle treatment to onset ≤ 6 hours=0,>6 hours=1.

The analysis revealed that hypothermia, CRRT

treatment, older age, higher APACHE II score at ICU admission, time from diagnosis of sepsis to hospital admission>1 hour, time from first bundle treatment to onset>6 hours, initial infection sites in the lungs, abdominal cavity, or skin/soft tissue, and higher lactate levels at ICU admission were independent risk factors for sepsis mortality (P<0.05). First symptoms of fever, initial infection site in the urinary system, longer length of ICU stay, and higher levels of creatinine, PCT, and fibrinogen at ICU admission were protective factors for sepsis mortality (P<0.05) **[Tab.5]**.

2.3 ROC Curve Analysis of Sepsis Mortality Risk Prediction Model

The binary logistic regression results showed that the mortality risk prediction model for sepsis patients was:

Z=−8.294−1.184×fever −3.039×initial urinary infection +1.236×hypothermia+1.493×CRRT+0.044×age +1.106×(time from diagnosis of sepsis to hospital admission> 1 hour) +1.553×(time from first bundle treatment to onset>6 hours) −0.151×(length of ICU stay) +1.168×(initial infection site is the lungs) +1.617×(initial infection site is the abdominal cavity) +1.823×(initial infection site is skin/soft tissue) −0.005×creatinine +0.182×lactate −0.022×PCT −0.294×fibrinogen +0.252×APACHE II

The ROC curve for the mortality risk model was plotted, and the AUC was 0.970, with a maximum Youden index of 0.826, sensitivity of 0.893, and specificity of 0.933. The ROC curve is shown in **Fig.1**.

Tab. 3 Univariate analysis of mortality factors in patients with sepsis (visits, bacterial culture, physical signs) [case (%)]

Indicators	Survive (n=165)	Death (n=121)	$\chi^2/t/Z$ value	P value
Referral	134(81.21)	85(70.25)	4.678	**0.031**
Time from first visit to onset of illness >6 h	93(56.36)	91(75.21)	10.802	**0.001**
Time from ICU admission to onset of illness>72 h	81(49.09)	89(73.55)	17.328	**<0.001**
Diagnosed with sepsis at the time of onset>24 h	135(81.82)	116(95.87)	12.830	**<0.001**
Diagnosed with sepsis at the time of admission>1 h	31(18.79)	73(60.33)	52.062	**<0.001**
Cluster therapy before admission to ICU	159(96.36)	114(94.21)	0.743	0.389
The time between the first bundle therapy and the onset of the disease>6 h	110(66.67)	101(83.47)	10.189	**0.001**
Bacterial culture				
Gram positive bacteria	17(10.30)	28(23.14)	8.677	**0.003**
Gram negative bacteria	42(25.45)	37(30.58)	0.917	0.338
Fungus	21(12.73)	24(19.83)	2.660	0.103
Heart rate ($\bar{x}$±s)	102.03 ± 22.88	111.95 ± 27.26	3.251	**0.001**
Systolic blood pressure [a]	102.00(86.00,122.00)	100.00(80.50, 121.00)	0.765	0.444
MAP [a]	77.00(63.00, 87.50)	75.00(59.50, 91.00)	0.800	0.424
Temperature at ICU admission			2.093	0.351
Too Low	15(9.09)	17(14.05)		
Normal	91(55.15)	67(55.37)		
Too High	59(35.76)	37(30.58)		
Low body temperature	64(38.79)	91(75.21)	37.298	**<0.001**
Urine output within 24 hours (mL/h) [a]	80.00(39.50, 138.50)	40.00(3.50, 99.00)	4.517	**<0.001**
Balance of inflow and outflow within 24 hours (mL) [a]	640.00(-58.00,1 582.50)	1 682.0(599.50,3 182.50)	5.203	**<0.001**

Note: [a] meant the data was represent in the form of $M(P_{25}, P_{75})$.

Tab. 4 Univariate analysis of mortality factors in patients with sepsis (laboratory indicators and treatment status) [$M(Q_L,Q_U)$]

Indicators	Survive (n=165)	Death (n=121)	$Z/t/\chi^2$ value	P value
Blood sugar	7.27(5.57, 11.23)	6.70(4.94, 10.50)	1.471	0.141
Lactic acid	1.93(1.25, 3.37)	4.86(2.37, 8.53)	7.344	**<0.001**
White blood cell	13.94(7.47, 21.49)	12.33(5.10, 19.66)	1.383	0.167
Hemoglobin ($\bar{x}$±s)	105.07 ± 26.81	100.11 ± 28.68	1.500	0.135
Platelet	85.00(40.00, 154.50)	91.00(34.50, 175.00)	0.127	0.899
Albumin ($\bar{x}$±s)	28.39 ± 5.88	24.96 ± 6.56	4.635	**<0.001**
Total bilirubin	14.70(7.80, 26.30)	15.70(8.75, 46.35)	1.766	0.077
Urea	12.59(8.13, 18.35)	13.16(9.15, 21.90)	1.245	0.213
Creatinine	167.00(104.00, 301.00)	162.00(92.00, 236.50)	1.395	0.163
PCT	34.42(4.25, 100.00)	7.47(2.60, 39.46)	3.717	**<0.001**
BNP	4 005.00(1 524.50,16 211.00)	4 128.00(1 475.50, 12 382.00)	0.365	0.715
hs-TnI	38.20(6.95, 306.70)	88.20(26.40, 446.65)	2.520	**0.012**
Hs-CRP	158.00(85.05, 246.60)	119.20(48.25, 186.20)	3.210	**0.001**
IL-6	389.10(69.00,1 648.48)	1 648.48(254.78, 5 000.00)	3.833	**<0.001**
Prothrombin time	16.30(15.15, 18.35)	18.60(15.75, 22.95)	3.948	**<0.001**
Fibrinogen	4.81(3.18, 6.37)	3.28(2.00, 4.84)	4.802	**<0.001**
APTT	51.00(43.65, 60.55)	50.10(43.90, 73.80)	0.918	0.358
D-dimer	6.04(2.47, 10.83)	5.28(2.39, 14.00)	0.179	0.858
APACHE II rating	16.00(11.50, 20.00)	27.00(20.50, 33.00)	10.416	**<0.001**
Using a ventilator to treat [case (%)]	31(18.79)	112(92.56)	151.975	**<0.001**
Duration of ventilator (h)	0.00(0.00, 0.00)	44.00(14.00, 105.00)	10.641	**<0.001**
Perform CRRT treatment [case (%)]	77(46.67)	93(76.86)	26.396	**<0.001**
Using vasoactive drugs [case (%)]	102(61.82)	118(97.52)	50.126	**<0.001**
Length of ICU stay (d)	6.00(4.00, 9.00)	4.00(2.00, 7.00)	4.297	**<0.001**

Tab. 5 Logistic regression analysis results

Indicators	*β*	*SE*	*Wald X²*	*P*	*OR*	95%*CI*	
						Lower	Upper
Fever	-1.184	0.602	3.862	0.049	0.306	0.094	0.997
Urinary tract infection	-3.039	1.165	6.808	0.009	0.048	0.005	0.469
Low body temperature	1.236	0.546	5.125	0.024	3.443	1.181	10.040
Perform CRRT treatment	1.493	0.603	6.133	0.013	4.449	1.365	14.499
Age	0.044	0.018	5.735	0.017	1.045	1.008	1.083
Diagnosed with sepsis at the time of admission	1.106	0.526	4.416	0.036	3.023	1.077	8.480
The time between the first bundle therapy and the onset of the disease	1.553	0.622	6.240	0.012	4.727	1.397	15.992
ICU length of stay	-0.151	0.042	13.027	0.000	0.860	0.792	0.933
pulmonary infection	1.168	0.595	3.854	0.049	3.215	1.002	10.316
Abdominal infection	1.617	0.778	4.317	0.038	5.040	1.096	23.177
Skin and soft tissue infections	1.823	0.925	3.882	0.049	6.188	1.010	37.932
Creatinine	-0.005	0.002	8.658	0.003	0.995	0.992	0.998
Lactic acid	0.182	0.074	6.035	0.014	1.200	1.037	1.387
PCT	-0.022	0.008	7.469	0.006	0.979	0.963	0.994
Fibrinogen	-0.294	0.131	5.023	0.025	0.745	0.576	0.964
APACHE II rating	0.252	0.045	31.186	0.000	1.287	1.178	1.406
Constant	-8.294	1.653	25.170	0.000	0.000		

3 Discussion

In this study, the initial infection sites in the lungs or abdominal cavity were identified as risk factors for death in sepsis patients, while the urinary system as the initial infection site served as a protective factor against sepsis-related mortality. This finding is similar to results from an overseas study [6]. The study also found that patients with skin and soft tissue infections had higher mortality rate (57.69%). Peetermans *et al.* [7] found that early and correct application of antibiotic therapy, along with appropriate local skin care, could significantly reduce the mortality rate in patients with skin and soft tissue infections. Shimazui *et al.* [8] reported that hypothermia is a risk factor for death in sepsis patients, which was consistent with the results of this study. Hypothermia can cause metabolic disturbances and multiple organ dysfunction [9]. Clinically, it is important to manage patient body temperature to reduce and prevent hypothermia [10]. Some studies have shown that advanced age is a risk factor for sepsis-related death [11], which is also supported by the findings of this study.

The presence of fever as an initial symptom was found to be a protective factor for the prognosis of sepsis, consistent with the results of Beadle *et al.* [12]. An elevated body temperature can inhibit the growth of pathogens [13]. Patients who do not develop fever or even experience hypothermia during the early stages of illness should be closely monitored. This study also found that the risk of death in sepsis patients diagnosed more than 1 hour after admission was 3.023 times higher than in those diagnosed within 1 hour. Early diagnosis is essential for reducing sepsis mortality [14]. Furthermore, the study found that the death risk for patients receiving initial bundle therapy more than 6 hours after onset was 4.727 times higher than for those treated within 6 hours. This finding aligns with international research [15]. This study confirms that rapidly implementing effective management strategies is crucial for improving patient prognosis.

In this study, higher lactate levels and higher APACHE II scores upon ICU admission were independent risk factors for sepsis-related death, consistent with findings from both domestic and international studies [16-17]. The study also found that higher creatinine levels upon ICU admission were a protective factor for sepsis mortality. Some studies have shown that high creatinine levels at the initiation of CRRT serve as a protective factor for survival in sepsis patients [18]. Therefore, it is important not to overlook elevated creatinine levels upon ICU admission, as delays in treatment may have adverse effects. This study also found that higher PCT levels upon ICU admission were a protective factor for sepsis prognosis. Increasingly, studies are exploring PCT as an important tool for diagnosing and managing sepsis patients [19]. This study also confirms that high PCT levels can aid in the early diagnosis of sepsis. Additionally, a decrease in fibrinogen levels has been associated with higher mortality rates in sepsis patients [20], and this study had a similar result.

The study found that longer ICU stays were a protective factor for the prognosis of sepsis, which is consistent with the results of Chen *et al.* [21]. Sepsis often has an acute onset, progresses rapidly, and has a high early mortality rate. Therefore, early intervention and intensive care are crucial to achieving the goal of reducing mortality. This study also identified CRRT treatment as an independent risk factor for sepsis-related death [22]. Similar results were reported by Fang *et al.* [23]. The higher mortality rate in the CRRT group suggests that these patients are more critically ill and require CRRT treatment [24]. Thus, early initiation of CRRT in patients with indications for the procedure is essential, and proper temperature management should be implemented to prevent and reduce hypothermia [10,25].

This study has some limitations. It is a single-center, retrospective study; additionally, for data integrity, only adult sepsis patients admitted to a comprehensive ICU were included. Further multi-center, prospective studies are needed to further investigate the factors influencing sepsis-related mortality.

In conclusion, healthcare providers should actively implement measures to prevent increased mortality risks in sepsis patients. When mortality risk has already increased, timely symptomatic treatment and nursing care should be provided. Furthermore, proactive prevention of mortality risk should be emphasized, especially by addressing pre-hospital risk factors to reduce and prevent adverse outcomes. Additionally, the sepsis mortality risk prediction model developed in this study demonstrates good predictive ability and can provide valuable reference for clinical practice.

The authors report no conflict of interest

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·论　著·

脓毒症死亡影响因素分析

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摘要：目的　构建脓毒症死亡风险预测模型，以期为提高脓毒症患者死亡风险预警、改善脓毒症患者结局提供参考。**方法**　回顾性收集 2019 年 1 月至 2022 年 5 月华中科技大学同济医学院附属同济医院综合 ICU 收治的符合诊断标准的脓毒症患者 286 例的资料，采用 t 检验、χ^2 检验和 Mann-Whitney U 检验对脓毒症患者的死亡风险进行单因素分析，进一步进行多因素分析，并构建脓毒症死亡风险预测模型。**结果**　统计患者入住 ICU 后 28 d 存活情况，286 例脓毒症患者，生存 165 例（57.69%），死亡 121 例（42.31%）。初始感染部位为肺部、腹腔、皮肤软组织和泌尿系统，诊断为脓毒症距入院时间、首次集束化治疗距发病时间、年龄、入住 ICU 时的乳酸值和 APACHE Ⅱ评分、发生低体温、行连续性肾脏替代疗法（CRRT）治疗、首发症状有发热、ICU 住院天数，以及入住 ICU 时肌酐、降钙素原、纤维蛋白原水平是脓毒症患者死亡的独立影响因素（P<0.05）。脓毒症患者死亡风险预测模型的 ROC 曲线下面积（AUC）为 0.970，敏感度为 0.893，特异度为 0.933，最大约登指数为 0.826。**结论**　对脓毒症患者死亡风险预防还需关口前移，重视患者院前死亡风险因素，把握确诊性治疗前的病情变化，以减少和避免不良结局。本研究初步构建的脓毒症患者死亡风险预测模型具有较好的预测能力，能够为临床工作提供一定的参考价值。

关键词： 脓毒症；死亡；风险预测模型；连续性肾脏替代疗法；降钙素原；纤维蛋白原
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Analysis of risk factors for death in patients with sepsis

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Abstract: Objective　To construct a death risk prediction model of sepsis, in order to provide reference for improving the early warning of death risk and improving the outcome of sepsis patients. **Methods**　The data of 286 sepsis patients who met the diagnostic criteria in the comprehensive ICU of Tongji Hospital, Tongji Medical College of Huazhong University of Science and Technology from January 2019 to May 2022 were retrospectively collected. The t test, chi-square test and Mann-Whitney U test were used to conduct univariate analysis on the death risk of sepsis patients, and then multivariate analysis was carried out, and a prediction model of sepsis death risk was established. **Results**　The survival status of 28 days after admission to ICU was calculated. Of 286 patients with sepsis, 165 (57.69%) survived and 121 (42.31%) died. The initial infection sites were lung, abdominal cavity, skin and soft tissue, urinary system, the time between diagnosis of sepsis and admission, time from onset to first cluster therapy, age, lactic acid level and APACHE Ⅱ score at admission to ICU, occurrence of hypothermia, continuous renal replacement therapy (CRRT), first symptoms of fever at onset, length of stay in ICU, the levels of creatinine, procalcitonin and fibrinogen at ICU admission were independent influencing factors of death in sepsis patients (P<0.05). The area under the ROC curve of the death risk prediction model for sepsis patients was 0.970, with a sensitivity of 0.893, a specificity of 0.933, and a maximum

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Youden index of 0.826. **Conclusion** The prevention focus of death risk in sepsis patients needs to be moved forward, the risk factors of pre-hospital death of patients should be paied attention to, the changes in the condition before confirmatory treatment should be grasped, in order to reduce and avoid adverse outcomes. In addition, the preliminarily constructed death risk prediction model for sepsis patients in this study has good predictive ability, and can provide certain reference value in clinical work.

Keywords: Sepsis; Death; Risk prediction model; Continuous renal replacement therapy; Procalcitonin; Fibrinogen

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脓毒症是一种临床上较常见的全身炎症综合征，随着病情进展，可导致患者脏器功能障碍、休克，死亡率较高[1]。全球每年有 4 890 万人被诊断为脓毒症，约 1 100 万人死亡[2]。我国的脓毒症死亡率约为 33.6%[3]。脓毒症仍是威胁全球健康的主要原因，不仅严重危害人民健康，且与社会经济发展密切相关[4]。

目前脓毒症死亡影响因素研究涵盖内容多，涉及面广泛，但更倾向于研究特定人群（如老人、新生儿）和特定病种（如泌尿系结石相关性脓毒症），而确诊性治疗前的资料与患者的治疗密切相关，可影响患者预后。故本研究拟纳入综合 ICU 收治的脓毒症成人患者，结合院前指标、诊断及治疗相关指标，构建死亡风险预测模型，以期提高脓毒症患者死亡风险预警、制定脓毒症患者预后管理策略、改善患者结局提供依据。

1　资料与方法

1.1　*临床资料*　采用便利抽样法，选取 2019 年 1 月 1 日至 2022 年 5 月 31 日华中科技大学同济医学院附属同济医院综合 ICU 收治的脓毒症患者 286 例为研究对象。本研究经过医院医学伦理委员会审核通过（TJ-IRB20220711）。纳入标准：（1）符合脓毒症诊断标准[5]；（2）年龄≥18 周岁。排除标准：（1）病历资料缺如或重复者；（2）诊断为新型冠状病毒感染的患者。最终共纳入研究对象 286 例。

1.2　*方法*　入住 ICU 的脓毒症患者均立即监测生命体征，采集血标本。此外，收集患者的一般资料（性别、年龄、居住地、吸烟史、饮酒史、初始感染部位、基础疾病），院前情况及就诊情况（有无转诊、首发症状、首次就诊距发病时间、入 ICU 距发病时间、诊断为脓毒症距发病时间、诊断为脓毒症距入院时间、入 ICU 前有无集束化治疗、首次集束化治疗距发病时间），患者入住 ICU 时的生命体征［体温、心率、呼吸、收缩压、平均动脉压（MAP）］，入住 ICU 时的实验室指标［血小板、血红蛋白、白细胞、白蛋白、活化部分凝血活酶时间（APTT）、凝血酶原时间（PT）、纤维蛋白原、降钙素原（PCT）、超敏 C 反应蛋白、B 型利钠肽（BNP）、高敏心肌肌钙蛋白 I（hs-TnI）、D-二聚体、白细胞介素 6（IL-6）、乳酸、血糖、总胆红素、尿素、肌酐］，入 ICU 时急性生理与慢性健康状况Ⅱ（APACHEⅡ）评分，入 ICU 24 h 内平均尿量，细菌培养情况（血培养、尿培养、痰培养及引流液培养），住院期间是否有低体温（腋温<36 ℃）及治疗情况［包括连续性肾脏替代疗法（CRRT）治疗、机械通气、血管活性药物使用、24 h 出入量、ICU 住院天数］。

1.3　*统计学方法*　收集到的数据应用 SPSS 22.0 软件进行分析。其中符合正态分布的计量资料用 $\bar{x}\pm s$ 表示，采用两独立样本 t 检验；不符合正态分布的计量资料用 $M(Q_L, Q_U)$ 描述，比较采用非参数检验的 Mann-Whitney U 检验。计数资料用例（%）表示，比较采用 χ^2 检验。纳入单因素分析有统计学意义的指标及临床有意义的指标，进行 logistic 回归分析，筛选出预后危险因素和保护性因素，构建脓毒症死亡风险预测模型，并绘制 ROC 曲线，计算曲线下面积（AUC）及敏感度、特异度。P<0.05 为差异有统计学意义。

2　结　果

2.1　*脓毒症死亡相关因素的单因素分析*　286 例患者中，121 例死亡，入住 ICU 后 28 d 死亡率为 42.31%。生存组与死亡组在年龄和居住地，基础疾病有肿瘤或心脏病，初始感染部位为肺部或腹腔，首发症状有发热、意识障碍或呼吸系统症状，转诊、首次就诊距发病时间>6 h、入 ICU 距发病时间>72 h、诊断为脓毒症距发病时间>24 h、诊断为脓毒症距入院时间>1 h、首次集束化治疗距发病时间>6 h，革兰阳性菌检出率、心率、低体温发生率、入 ICU 24 h 内尿量及出入量平衡情况，及入 ICU 时乳酸、白蛋白、PCT、超敏 C 反应蛋白、hs-TnI、IL-6、PT、纤维蛋白原、APACHEⅡ评分、呼吸机使用率、呼吸机时长、CRRT 治疗率、血管活性药物使用率及住院天数，差异有统计学意义（P<0.05）。见表 1 至表 4。

表 1　脓毒症死亡相关因素(一般资料)的单因素分析　[例(%)]

Tab. 1　Univariate analysis of mortality factors in patients with sepsis (general data)　[case (%)]

因素		生存(n=165)	死亡(n=121)	Z/χ^2 值	P 值
年龄(岁)[a]		57.00(49.00, 65.00)	63.00(54.00, 73.00)	3.474	0.001
性别	男	84(50.91)	64(52.89)	0.110	0.740
	女	81(49.09)	57(47.11)		
居住地	城市	74(44.85)	75(61.98)		
	乡镇	29(17.58)	15(12.40)	8.220	0.016
	农村	62(37.57)	31(25.62)		
吸烟史	无	120(72.73)	98(80.99)	2.631	0.105
	有	45(27.27)	23(19.01)		
饮酒史	无	138(83.64)	103(85.12)	0.117	0.733
	有	27(16.36)	18(14.88)		
基础疾病					
呼吸系统疾患	无	156(94.55)	107(88.43)	3.531	0.060
	有	9(5.45)	14(11.57)		
高血压	无	112(67.88)	83(68.60)	0.017	0.898
	有	53(32.12)	38(31.40)		
肝肾疾患	无	115(69.70)	84(69.42)	0.003	0.960
	有	50(30.30)	37(30.58)		
糖尿病	无	129(78.18)	98(80.99)	0.337	0.562
	有	36(21.82)	23(19.01)		
肿瘤	无	139(84.24)	89(73.55)	4.933	0.026
	有	26(15.76)	32(26.45)		
心脏病	无	151(91.52)	99(81.82)	5.966	0.015
	有	14(8.48)	22(18.18)		

注:[a] 表示数据形式为 $M(Q_L,Q_U)$。

表 2　脓毒症死亡相关因素(初始感染部位和首发症状)的单因素分析　[例(%)]

Tab. 2　Univariate analysis of mortality factors in patients with sepsis (initial infection site and first symptoms)　[case (%)]

因素		生存(n=165)	死亡(n=121)	χ^2 值	P 值
肺部感染	否	123(74.55)	71(58.68)	8.055	0.005
	是	42(25.45)	50(41.32)		
泌尿系感染	否	130(78.79)	116(95.87)	16.928	<0.001
	是	35(21.21)	5(4.13)		
腹腔感染	否	148(89.70)	96(79.34)	5.978	0.014
	是	17(10.30)	25(20.66)		
皮肤软组织感染	否	154(93.33)	106(87.60)	2.773	0.096
	是	11(6.67)	15(12.40)		
胃肠道感染	否	149(90.30)	117(96.69)	4.384	0.036
	是	16(9.70)	4(3.31)		
血流感染	否	159(96.36)	120(99.17)	1.282	0.258
	是	6(3.64)	1(0.83)		
颅内感染	否	164(99.39)	120(99.17)		1.000[a]
	是	1(0.61)	1(0.83)		
首发症状					
发热	无	85(51.52)	96(79.34)	23.259	<0.001
	有	80(48.48)	25(20.66)		
腹部及消化系统症状	无	110(66.67)	75(61.98)	0.670	0.413
	有	55(33.33)	46(38.02)		
腹部外的部位疼痛	无	135(81.82)	97(80.17)	0.125	0.724
	有	30(18.18)	24(19.83)		
意识障碍	无	160(96.97)	103(85.12)	13.246	<0.001
	有	5(3.03)	18(14.88)		
呼吸系统症状	无	149(90.30)	95(78.51)	7.746	0.005
	有	16(9.70)	26(21.49)		

注:[a] 为采用 Fisher 确切概率法。

表 3　脓毒症死亡相关因素(就诊、细菌培养、体征)的单因素分析　[例(%)]

Tab. 3　Univariate analysis of mortality factors in patients with sepsis (visits, bacterial culture, physical signs)　[case (%)]

因素		生存(n=165)	死亡(n=121)	$\chi^2/t/z$ 值	P 值
转诊	无	31(18.79)	36(29.75)	4.678	0.031
	有	134(81.21)	85(70.25)		
首次就诊距发病时间	≤6 h	72(43.64)	30(24.79)	10.802	0.001
	>6 h	93(56.36)	91(75.21)		
入 ICU 距发病时间	≤72 h	84(50.91)	32(26.45)	17.328	<0.001
	>72 h	81(49.09)	89(73.55)		
诊断为脓毒症距发病时间	≤24 h	30(18.18)	5(4.13)	12.830	<0.001
	>24 h	135(81.82)	116(95.87)		
诊断为脓毒症距入院时间	≤1 h	134(81.21)	48(39.67)	52.062	<0.001
	>1 h	31(18.79)	73(60.33)		
入ICU 前集束化治疗	无	6(3.64)	7(5.79)	0.743	0.389
	有	159(96.36)	114(94.21)		
首次集束化治疗距发病时间	≤6 h	55(33.33)	20(16.53)	10.189	0.001
	>6 h	110(66.67)	101(83.47)		
细菌培养结果					
革兰阳性菌	无	148(89.70)	93(76.86)	8.677	0.003
	有	17(10.30)	28(23.14)		
革兰阴性菌	无	123(74.55)	84(69.42)	0.917	0.338
	有	42(25.45)	37(30.58)		
真菌	无	144(87.27)	97(80.17)	2.660	0.103
	有	21(12.73)	24(19.83)		
心率[a]		102.03±22.88	111.95±27.26	3.251	0.001
收缩压[b]		102.00(86.00, 122.00)	100.00(80.50, 121.00)	0.765	0.444
MAP[b]		77.00(63.00, 87.50)	75.00(59.50, 91.00)	0.800	0.424
入 ICU 时体温	过低	15(9.09)	17(14.05)	2.093	0.351
	正常	91(55.15)	67(55.37)		
	过高	59(35.76)	37(30.58)		
低体温	否	101(61.21)	30(24.79)	37.298	<0.001
	是	64(38.79)	91(75.21)		
入ICU 24 h 内尿量(mL/h)[b]		80.00(39.50, 138.50)	40.00(3.50, 99.00)	4.517	<0.001
入ICU 24 h 内出入量平衡情况(mL)[b]		640.00(−58.00, 1 582.50)	1 682.0(599.50, 3 182.50)	5.203	<0.001

注:[a] 表示数据形式为 $\bar{x}\pm s$;[b] 表示数据形式为 $M(Q_L,Q_U)$。

2.2　脓毒症死亡相关因素 logistic 回归分析　将死亡作为因变量,单因素分析有意义的指标并结合临床有意义的结果作为自变量,进行多因素 logistic 回归分析。赋值方式:发病首发症状无发热=0,有发热=1;初始感染部位不是肺部=0,是肺部=1;初始感染部位不是腹腔=0,是腹腔=1;初始感染部位不是皮肤软组织=0,是皮肤软组织=1;初始感染部位不是泌尿系统=0,是泌尿系统=1;住院期间无低体温=0,有低体温=1;未行 CRRT 治疗=0,行 CRRT 治疗=1;诊断为脓毒症距入院时间≤1 h=0,>1 h=1;首次集束化治疗距发病时间≤6 h=0,>6 h=1。多因素分析显示,低体温、行 CRRT 治疗、年龄较大、入 ICU 时 APACHEⅡ评分较高,诊断为脓毒症距入院时间>

1 h,首次集束化治疗距发病时间>6 h,初始感染部位为肺部、腹腔、皮肤软组织,入 ICU 时乳酸值较高,均为脓毒症死亡的独立危险因素(P<0.05)。首发症状有发热、初始感染部位为泌尿系统、ICU 住院天数较长,以及入住 ICU 时肌酐、PCT、纤维蛋白原水平高为脓毒症死亡的保护性因素(P<0.05)。见表 5。

表 4　脓毒症死亡相关因素(实验室指标及治疗情况)的单因素分析　[$M(Q_L,Q_U)$]

Tab. 4　Univariate analysis of mortality factors in patients with sepsis (laboratory indicators and treatment status)　[$M(Q_L, Q_U)$]

因素		生存(n=165)	死亡(n=121)	$Z/t/\chi^2$ 值	P 值
血糖(mmol/L)		7.27(5.57, 11.23)	6.70(4.94, 10.50)	1.471	0.141
乳酸(mmol/L)		1.93(1.25, 3.37)	4.86(2.37, 8.53)	7.344	<0.001
白细胞($\times10^9$/L)		13.94(7.47, 21.49)	12.33(5.10, 19.66)	1.383	0.167
血红蛋白(g/L)[a]		105.07±26.81	100.11±28.68	1.500	0.135
血小板($\times10^9$/L)		85.00(40.00, 154.50)	91.00(34.50, 175.00)	0.127	0.899
白蛋白(g/L)[a]		28.39±5.88	24.96±6.56	4.635	<0.001
总胆红素(μmol/L)		14.70(7.80, 26.30)	15.70(8.75, 46.35)	1.766	0.077
尿素(mmol/L)		12.59(8.13, 18.35)	13.16(9.15, 21.90)	1.245	0.213
肌酐(μmol/L)		167.00(104.00, 301.00)	162.00(92.00, 236.50)	1.395	0.163
PCT(ng/mL)		34.42(4.25, 100.00)	7.47(2.60, 39.46)	3.717	<0.001
BNP(pg/mL)		4 005.00(1 524.50, 16 211.00)	4 128.00(1 475.50, 12 382.00)	0.365	0.715
hs-TnI(pg/mL)		38.20(6.95, 306.70)	88.20(26.40, 446.65)	2.520	0.012
超敏 C 反应蛋白(mg/L)		158.00(85.05, 246.60)	119.20(48.25, 186.20)	3.210	0.001
IL-6(pg/mL)		389.10(69.00, 1 648.48)	1 648.48(254.78, 5 000.00)	3.833	<0.001
PT(s)		16.30(15.15, 18.35)	18.60(15.75, 22.95)	3.948	<0.001
纤维蛋白原(g/L)		4.81(3.18, 6.37)	3.28(2.00, 4.84)	4.802	<0.001
APTT(s)		51.00(43.65, 60.55)	50.10(43.90, 73.80)	0.918	0.358
D-二聚体(μg/mL)		6.04(2.47, 10.83)	5.28(2.39, 14.00)	0.179	0.858
APACHEⅡ评分		16.00(11.50, 20.00)	27.00(20.50, 33.00)	10.416	<0.001
使用呼吸机治疗[b]	否	134(81.21)	9(7.44)	151.975	<0.001
	是	31(18.79)	112(92.56)		
呼吸机时长(h)		0.00(0.00, 0.00)	44.00(14.00, 105.00)	10.641	<0.001
行 CRRT 治疗[b]	否	88(53.33)	28(23.14)	26.396	<0.001
	是	77(46.67)	93(76.86)		
使用血管活性药物[b]	否	63(38.18)	3(2.48)	50.126	<0.001
	是	102(61.82)	118(97.52)		
ICU 住院天数(d)		6.00(4.00, 9.00)	4.00(2.00, 7.00)	4.297	<0.001

注:[a] 表示数据形式为 $\bar{x}\pm s$;[b] 表示数据形式为例(%)。

表 5　Logistic 回归分析结果

Tab. 5　Logistic regression analysis results

变量	β	SE	$Wald\ \chi^2$	P 值	OR 值	95%CI	
						下限	上限
发热	−1.184	0.602	3.862	0.049	0.306	0.094	0.997
泌尿系感染	−3.039	1.165	6.808	0.009	0.048	0.005	0.469
低体温	1.236	0.546	5.125	0.024	3.443	1.181	10.040
行 CRRT 治疗	1.493	0.603	6.133	0.013	4.449	1.365	14.499
年龄	0.044	0.018	5.735	0.017	1.045	1.008	1.083
诊断为脓毒症距入院时间>1 h	1.106	0.526	4.416	0.036	3.023	1.077	8.480
首次集束化治疗距发病时间>6 h	1.553	0.622	6.240	0.012	4.727	1.397	15.992
ICU 住院天数	−0.151	0.042	13.027	<0.001	0.860	0.792	0.933
肺部感染	1.168	0.595	3.854	0.049	3.215	1.002	10.316
腹腔感染	1.617	0.778	4.317	0.038	5.040	1.096	23.177
皮肤软组织感染	1.823	0.925	3.882	0.049	6.188	1.010	37.932
肌酐	−0.005	0.002	8.658	0.003	0.995	0.992	0.998
乳酸	0.182	0.074	6.035	0.014	1.200	1.037	1.387
PCT	−0.022	0.008	7.469	0.006	0.979	0.963	0.994
纤维蛋白原	−0.294	0.131	5.023	0.025	0.745	0.576	0.964
APACHEⅡ评分	0.252	0.045	31.186	<0.001	1.287	1.178	1.406
常量	−8.294	1.653	25.170	<0.001			

2.3　脓毒症死亡风险预测模型的 ROC 曲线分析　二元 logistic 回归分析结果显示,脓毒症患者的死亡风险预测模型为 $Z=-8.294-1.184\times$首发症状有发热$-3.039\times$初始感染部位为泌尿系统$+1.236\times$低体温$+1.493\times$CRRT 治疗$+0.044\times$年龄$+1.106\times$诊断为脓毒症距入院时间>1 h$+1.553\times$首次集束化治疗距发病时间>6 h$-0.151\times$ICU 住院天数$+1.168\times$初始感染部位为肺部$+1.617\times$初始感染部位为腹腔$+1.823\times$初始感染部位为皮肤软组织$-0.005\times$肌酐值$+0.182\times$乳酸值$-0.022\times$PCT 值$-0.294\times$纤维蛋白原值$+0.252\times$APACHEⅡ评分。绘制死亡风险模型的 ROC 曲线,AUC 为 0.970,最大约登指数为 0.826,敏感度为 0.893,特异度为 0.933。ROC 曲线图见图 1。

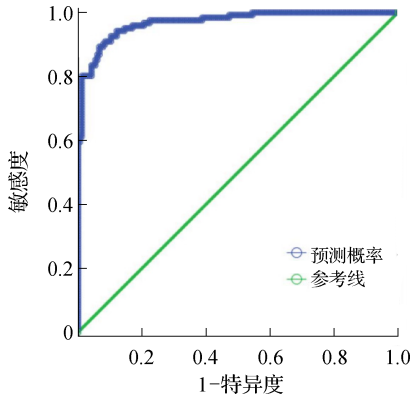

图 1　脓毒症死亡风险预测模型的 ROC 曲线
Fig. 1　ROC curve of death risk prediction model of sepsis

3　讨　论

本研究发现,初始感染部位为肺部或腹腔是脓毒症患者死亡的危险因素,初始感染部位为泌尿系统是脓毒症死亡的保护因素。这与国外的一项研究结果相似[6]。本研究发现皮肤软组织感染者死亡率也较高(57.69%)。Peetermans 等[7]发现,早期正确应用抗生素治疗并做好局部的皮肤护理,能够极大降低皮肤软组织感染患者死亡率。Shimazui 等[8]报道了低体温是脓毒症患者死亡的危险因素,本研究结果与之相一致。低体温可能引起代谢紊乱以及多器官功能障碍[9]。临床上需做好患者体温管理,减少和避免发生低体温[10]。有研究发现年龄较高是脓毒症死亡的危险因素[11],本研究也得出相同的结论。

首发症状有发热是脓毒症预后的保护因素,与 Beadle 等[12]的研究结果相似。宿主体温升高会抑制病原体的繁殖[13]。发病初期未出现发热甚至出现低体温的患者需引起重视。本研究发现,诊断为脓毒症距入院时间>1 h 的死亡风险是≤1 h 的 3.023 倍。降低脓毒症患者死亡率的前提是早期诊断[14]。本研究显示,首次集束化治疗距发病时间>6 h 的死亡风险是≤6 h 的 4.727 倍。这与国外研究相符[15]。本研究证实,快速、及时、高效地实施管理策略,是改善患者预后的关键措施。

本研究中,入 ICU 时的乳酸值和 APACHEⅡ评分较高均为脓毒症死亡的独立危险因素。这与国内外研究一致[16-17]。本研究还发现入 ICU 时的肌酐值较高为脓毒症死亡的保护因素。有研究发现 CRRT 启动时高肌酐水平为脓毒症患者存活的保护因素[18]。因此入 ICU 时肌酐值不高也需引起重视,以免延误治疗。越来越多的研究开始探讨 PCT 作为诊断和管理脓毒症患者的重要工具[19]。本研究也发现,高 PCT 值可帮助预测脓毒症预后。有研究显示纤维蛋白原降低,脓毒症死亡率会升高[20]。本研究与之结果一致。

本研究发现 ICU 住院天数较长为脓毒症预后的保护因素,与陈强等[21]的研究结果一致。脓毒症起病急,病情进展快,早期病死率高。因此在脓毒症患者入住 ICU 早期要更加重视,积极抢救,以达到降低死亡率的目标[22]。本研究中,行 CRRT 治疗是脓毒症患者死亡的独立危险因素。方俊杰等[23]得出了类似的结果。CRRT 组患者死亡率更高提示患者病情更重,更需要 CRRT 治疗[24]。因此对有 CRRT 指征的患者需尽早行 CRRT 治疗,且需做好保暖,减少和避免低体温发生[10,25]。

本研究尚有一些局限性。仅为单中心回顾性研究;且经前期调研及数据预收集,为保证数据的完整性,本课题均纳入入住成人综合 ICU 的脓毒症患者。接下来需开展多中心、前瞻性研究以进一步完善脓毒症患者死亡的影响因素。

综上所述,医护人员需积极采取措施预防脓毒症患者出现死亡风险增加的情况,当已经发生死亡风险增加时,需及时给予对症治疗和护理,同时对死亡风险预防还需关口前移,重视患者院前死亡风险因素监测,以期减少和避免不良结局。此外,本研究初步构建的脓毒症患者死亡风险预测模型具有较好的预测能力,能够在临床工作中提供一定的参考价值。

利益冲突　无

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