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· 论 著 ·

临床有创干预措施与脓毒症患者入院 28 d 内死亡的相关性

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[摘要] **目的** 探讨脓毒症患者住院期间临床有创干预措施及 24 h 内入院指标与入院 28 d 内死亡的相关性。**方法** 回顾性分析解放军总医院第一医学中心 2016 年 1 月至 2018 年 12 月收治的 112 例脓毒症患者的临床资料, 分析住院期间 4 项临床有创干预措施[机械通气、气管插管、连续肾脏替代疗法(CRRT)、深静脉置管]及可能影响脓毒症患者死亡的入院指标(包括人口统计学特征、生命体征、实验室指标等), 并以患者入院 28 d 的生存情况为结局变量, 比较生存组($n=81$)和死亡组($n=31$)之间上述指标的差异, 然后利用多因素 logistic 回归分析确定脓毒症患者入院 28 d 内死亡的独立危险因素。**结果** 两组患者在年龄、序贯器官衰竭评分、急性生理学和慢性健康状况 II (APACHE II) 评分、IL-6 水平、降钙素原水平、天冬氨酸转氨酶水平、CRRT、深静脉置管方面的差异均有统计学意义(P 均 <0.05)。多因素 logistic 回归分析结果显示, IL-6 水平升高($OR=1.001$, $P=0.011$)、降钙素原水平降低($OR=0.966$, $P=0.005$)、采用 CRRT($OR=6.846$, $P=0.002$)是脓毒症患者入院 28 d 内死亡的独立危险因素。**结论** IL-6 水平升高、降钙素原水平降低、住院期间使用 CRRT 的脓毒症患者入院 28 d 内死亡风险较高, 密切观察并动态监测这些因素有助于早期识别可能发生不良结局的脓毒症患者; 必不可少的机械通气、气管插管、CRRT、深静脉置管等临床有创干预的实施比例在死亡患者中较高, 临床医师应认真评估、准确把握其中的平衡点。

[关键词] 脓毒症; 预后; 危险因素; logistic 模型; 肾替代疗法

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Correlation between clinical invasive interventions and death within 28-day after admission in sepsis patients

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[Abstract] **Objective** To investigate the relationship between the clinical invasive interventions during hospitalization and the admission indicators within 24 hours with death within 28-day after admission in sepsis patients. **Methods** The clinical data of 112 sepsis patients who were admitted to the First Medical Center of Chinese PLA General Hospital from Jan. 2016 to Dec. 2018 were analyzed retrospectively. Four clinical invasive interventions (mechanical ventilation, tracheal intubation, continuous renal replacement therapy [CRRT] and deep vein catheterization) and admission indicators (including demographic characteristics, vital signs and laboratory indexes) that may have an impact on the death of sepsis patients were selected during hospitalization, and the 28-day survival of patients was taken as the outcome variable. The above parameters were compared between the survival group ($n=81$) and the death group ($n=31$), and the independent risk factors of sepsis death within 28-day after admission were determined by multivariate logistic regression analysis. **Results** There were statistically significant differences in age, the sequential organ failure assessment (SOFA) score, acute physiology and chronic health evaluation II (APACHE II) score, IL-6, procalcitonin, aspartate aminotransferase, CRRT and deep vein catheterization between the two groups (all $P<0.05$). The results of the multivariate logistic regression analysis revealed that high IL-6 level (odds ratio [OR] = 1.001, $P=0.011$), low procalcitonin level ($OR=0.966$, $P=0.005$) and CRRT ($OR=6.846$, $P=0.002$) were independent risk factors of death within 28-day after admission in sepsis patients. **Conclusion** Sepsis patients with increased IL-6 level, decreased procalcitonin level and CRRT during hospitalization have a higher risk of death within 28-day after admission. Close observation and dynamic monitoring of changes in IL-6, procalcitonin and renal function will be beneficial for early identification of septic patients who might have adverse clinical outcomes. The proportions of essential invasive interventions such as mechanical ventilation, tracheal intubation, CRRT, and deep venous catheterization are higher in dead

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patients, so clinicians need to carefully evaluate and accurately grasp the balance point.

[Key words] sepsis; prognosis; risk factors; logistic models; renal replacement therapy

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脓毒症是一种严重威胁生命健康的复杂疾病,其发病与宿主应对感染时的免疫反应失调有关,并且多伴多器官功能衰竭(multiple organ dysfunction syndrome, MODS),如果得不到及时处理往往会发展成死亡率更高的脓毒症休克^[1]。2017年的统计数据显示,全球每年新发脓毒症患者超过3 000万例,病死率更是高达36%~55%^[2],因此早期识别可能发生不良结局的脓毒症患者并积极采取防治措施将极大改善脓毒症患者的预后^[2-4]。对患者来说,临床有创干预治疗是一把双刃剑,既有利也有弊,不过当前的临床研究大多强调有创干预治疗的“利”,却忽略了可能对患者产生的“不利”之处。目前,脓毒症不良预后危险因素的研究主要集中在人口统计学特征及实验室指标^[5-7]方面,患者住院期间接受的临床有创干预措施与不良预后的相关性研究相对较少。本研究通过回顾性分析解放军总医院第一医学中心112例脓毒症患者的临床资料,纳入患者人口统计学特征、实验室指标和住院期间接受的4项临床有创干预性治疗措施,探讨临床有创治疗和脓毒症患者不良结局的相关性,寻找可能与脓毒症患者死亡相关的危险因素,为重症医学科和其他科室医师早期识别预后不佳脓毒症患者提供参考。

1 对象和方法

1.1 研究对象 回顾性连续收集2016年1月至2018年12月入住解放军总医院第一医学中心ICU的112例脓毒症患者的临床资料。纳入标准:(1)符合《脓毒症与脓毒症休克国际共识(第3版)》^[1]诊断标准;(2)临床资料和实验室检查数据完整;(3)年龄 ≥ 18 岁;(4)住院时间 ≥ 48 h。排除标准:(1)入院24 h内死亡;(2)中转住院时间 ≥ 72 h;(3)伴急性肾损伤或慢性肾功能衰竭;(4)伴自身免疫性疾病;(5)妊娠期及哺乳期妇女。

1.2 观察指标 收集患者入院时的人口统计学特征,血常规、血生物化学、凝血功能、动脉血气分析等指标,根据患者入院时的生理状况计算格拉斯哥昏迷评分(Glasgow coma score, GCS)、序贯

器官衰竭评估(sequential organ failure assessment, SOFA)评分、急性生理学及慢性健康状况II(acute physiology and chronic health evaluation II, APACHE II)评分,并统计患者住院期间机械通气、气管插管、连续肾脏替代疗法(continuous renal replacement therapy, CRRT)、深静脉置管4种临床干预措施的应用情况。

1.3 结局指标 以患者入院后28 d生存情况作为结局指标进行分析。从患者住院开始住院时间不足28 d的出院患者,通过电话随访28 d内的生存情况。

1.4 统计学处理 应用SPSS 24.0软件进行统计学分析。服从正态分布的计量资料以 $\bar{x} \pm s$ 表示,两组间比较采用独立样本 t 检验;计数资料以例数和百分数表示,组间比较采用 χ^2 检验。对 $P < 0.05$ 的变量通过向前似然法进行多因素logistic回归分析,确定患者入院28 d内死亡的独立危险因素。检验水准(α)为0.05。

2 结果

2.1 患者临床基线资料 本研究共纳入112例脓毒症患者,男75例(66.96%)、女37例(33.04%),年龄21~92岁,平均年龄(67.54 ± 16.42)岁,入院28 d生存患者共有81例,生存率为72.32%。根据患者28 d的生存情况分为两组:生存组男51例(62.96%)、女30例(37.04%),平均年龄(65.26 ± 14.89)岁;死亡组患者31例,其中男和女分别为24例(77.42%)和7例(22.58%),平均年龄(73.48 ± 18.88)岁;两组患者在年龄、SOFA评分、APACHE II评分方面的差异均有统计学意义(P 均 < 0.05),两组患者在性别、BMI、GCS方面的差异均无统计学意义(P 均 > 0.05)。见表1。

2.2 两组患者实验室指标比较 死亡组患者的IL-6、天冬氨酸转氨酶(aspartate aminotransferase, AST)水平高于生存组,降钙素原水平低于生存组,差异均有统计学意义(P 均 < 0.05),其余实验室指标在两组间差异均无统计学意义(P 均 > 0.05)。见表2。

表1 生存组与死亡组脓毒症患者临床资料比较

Tab 1 Comparison of clinical data of sepsis patients between survival group and death group

Characteristic	Survival group <i>N</i> =81	Death group <i>N</i> =31	Statistic	<i>P</i> value
Age (year), $\bar{x} \pm s$	65.26 ± 14.89	73.48 ± 18.88	<i>t</i> = -2.423	0.017
Gender <i>n</i> (%)			χ^2 = 2.118	0.148
Male	51 (62.96)	24 (77.42)		
Female	30 (37.04)	7 (22.58)		
BMI (kg·m ⁻²), $\bar{x} \pm s$	24.09 ± 3.87	22.70 ± 4.11	<i>t</i> = 1.668	0.098
GCS $\bar{x} \pm s$	13.06 ± 1.71	11.60 ± 1.94	<i>t</i> = 4.119	0.081
SOFA $\bar{x} \pm s$	6.28 ± 2.90	7.61 ± 3.55	<i>t</i> = -2.035	0.044
APACHE II $\bar{x} \pm s$	12.43 ± 5.05	16.84 ± 5.55	<i>t</i> = -4.019	<0.001

BMI: Body mass index; GCS: Glasgow coma score; SOFA: Sequential organ failure assessment; APACHE II: Acute physiology and chronic health evaluation II

表2 生存组与死亡组脓毒症患者实验室指标比较

Tab 2 Comparison of laboratory indicators of sepsis patients between survival group and death group

Characteristic	Survival group <i>n</i> =81	Death group <i>n</i> =31	<i>t</i> value	<i>P</i> value
RBC (L ⁻¹ , ×10 ¹²)	3.46 ± 0.67	3.32 ± 0.69	0.970	0.334
WBC (L ⁻¹ , ×10 ⁹)	14.22 ± 8.89	15.01 ± 8.21	0.469	0.640
Hemoglobin (g·L ⁻¹)	106.23 ± 20.91	98.81 ± 21.08	1.678	0.096
IL-6 (pg·mL ⁻¹)	300.77 ± 94.17	1 166.44 ± 172.64	-2.645	0.012
CRP (mg·L ⁻¹)	11.61 ± 8.13	12.39 ± 8.28	-0.453	0.652
Procalcitonin (ng·mL ⁻¹)	44.52 ± 49.63	17.81 ± 25.09	3.750	<0.001
ALT (U·L ⁻¹)	83.03 ± 18.98	138.50 ± 32.53	-0.897	0.375
AST (U·L ⁻¹)	115.13 ± 19.33	318.86 ± 92.43	-1.217	0.016
Serum creatinine (μmol·L ⁻¹)	132.17 ± 119.90	140.38 ± 80.37	-0.352	0.726
BUN (mmol·L ⁻¹)	11.50 ± 7.78	12.78 ± 7.26	-0.795	0.428
D-dimer (μg·L ⁻¹)	5.56 ± 5.13	5.62 ± 5.08	-0.058	0.954
FIB (g·L ⁻¹)	5.51 ± 3.46	4.41 ± 2.01	0.858	0.393
PaCO ₂ (mmHg)	32.88 ± 7.31	35.82 ± 10.64	-1.500	0.140
PaO ₂ (mmHg)	100.87 ± 55.67	109.06 ± 56.19	-0.736	0.463
pH	7.43 ± 0.73	7.41 ± 0.74	0.880	0.381
Lactic acid (mmol·L ⁻¹)	3.25 ± 1.31	3.15 ± 2.61	0.057	0.954

1 mmHg=0.133 kPa. RBC: Red blood cell; WBC: White blood cell; IL-6: Interleukin 6; CRP: C-reactive protein; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; FIB: Fibrinogen; PaCO₂: Arterial partial pressure of carbon dioxide; PaO₂: Arterial partial pressure of oxygen

2.3 两组患者临床干预措施比较 81例生存组患者实施机械通气19例(23.46%),气管插管4例(4.94%),CRRT 36例(44.44%),深静脉置管58例(71.60%);31例死亡组患者实施机械通气12例(38.71%),气管插管4例(12.90%),CRRT 27例(87.10%),深静脉置管29例(93.55%)。死亡组患者的4项临床有创干预实施的比例均高于生存组,其中两组间CRRT ($\chi^2=16.573$, $P<0.001$)

和深静脉置管 ($\chi^2=6.226$, $P=0.013$) 的差异有统计学意义。

2.4 患者入院28 d内死亡危险因素的多因素 logistic 回归分析结果 运用向前似然法对上述8项 $P<0.05$ 的变量进行多因素 logistic 回归分析,结果(表3)显示降钙素原水平降低、IL-6水平升高和采用CRRT是脓毒症患者入院28 d内死亡的独立危险因素 (P 均 <0.05)。

表3 脓毒症患者入院28 d内死亡危险因素的多因素 logistic 回归分析

Tab 3 Multivariate logistic regression analysis of risk factors of death within 28-day after admission in sepsis patients

Variable	<i>B</i>	<i>SE</i>	<i>Wald</i>	<i>df</i>	<i>OR</i> (95% <i>CI</i>)	<i>P</i> value
Procalcitonin	-0.035	0.012	8.046	1	0.966 (0.943, 0.989)	0.005
IL-6	0.001	0.000	6.457	1	1.001 (1.000, 1.001)	0.011
CRRT	1.924	0.625	9.485	1	6.846 (2.013, 23.295)	0.002

IL-6: Interleukin 6; CRRT: Continuous renal replacement therapy; *B*: Regression coefficient; *SE*: Standard error; *df*: Degree of freedom; *OR*: Odds ratio; *CI*: Confidence interval

3 讨论

“拯救脓毒症运动”致力于降低脓毒症的发病率和死亡率,自2002年启动以来为全球危重症领域医务工作者提供了救治脓毒症患者的指南和规范,最新版指南将既往的3~6 h的集束化治疗时间窗缩短到1 h,更加强调了早期救治脓毒症患者的重要性^[3,8]。早期对脓毒症患者采取临床干预措施是提高患者生存率的关键,但这些措施均是侵入性有创手段,可能会加重患者的免疫功能紊乱。Ziesmann等^[9]指出,诱发炎症的因素、宿主免疫反应、临床干预治疗措施是脓毒症患者发生MODS必不可少的三大因素。CRRT是治疗急性肾损伤(acute kidney injury, AKI)和慢性肾功能衰竭常用的方法,不仅可以有效清除机体产生的肌酐、尿素氮等代谢废物,而且可以清除血液中的炎症介质、增强机体的免疫功能,因此对于伴有急性或慢性肾功能不全的患者,CRRT可能是维持其生命必不可少的治疗措施之一^[10-11]。本研究结果发现,使用CRRT的脓毒症患者死亡风险是非使用者的6.846倍。究其原因,一方面可能是需要CRRT治疗的脓毒症患者在住院期间发生了AKI,肾脏作为脓毒症比较容易累及且较早发生损伤的器官之一,一旦发生急性或慢性功能不全,那么脓毒症患者的死亡率将由45.2%上升到74.5%^[12]。脓毒症患者并发AKI与多种机制密切相关,包括肾脏缺血再灌注损伤、炎性因子大量聚集、凝血纤溶功能紊乱、氧化应激损伤等^[13]。另一方面,作为一种有创干预措施,CRRT改善脓毒症患者症状的同时也会存在导管相关性感染、低体温、电解质酸碱平衡紊乱、营养丢失等并发症,将会严重危及脓毒症患者的生命。总之,根据脓毒症患者住院期间CRRT的使用与否预测其发生不良结局的风险,同时应该密切关注脓毒症患者肾脏功能的动态变化,及早恢复患者的肾脏功能,降低住其院期间AKI的发生

率。除了CRRT,本研究结果还发现死亡组患者气管插管、机械通气和深静脉置管等有创干预措施的实施比例高于生存组;CRRT和深静脉置管在两组间的差异均有统计学意义(P 均 <0.05),与既往研究^[14-15]结果一致。Goligher等^[16]指出机械通气造成了患者膈肌萎缩和功能障碍,而深静脉置管增加了导管相关感染发生的风险,另一方面,气管插管、机械通气和深静脉置管的实施也从侧面反映患者病情较重。

降钙素原是反映机体炎症水平的常用指标,在感染性疾病患者中其浓度会增加。Wacker等^[17]研究发现,降钙素原是早期诊断脓毒症发生的一种有效生物标志物,同时综合考虑患者的病史和体格检查、微生物学检查结果等。Arora等^[18]收集了脓毒症存活患者和死亡患者降钙素原水平的临床数据并进行了meta分析,发现脓毒症早期存活患者的降钙素原水平低于脓毒症死亡患者,因此认为降钙素原水平升高可能是脓毒症患者死亡的危险因素。本研究结果与此相反,即随着降钙素原水平升高脓毒症患者的死亡风险反而降低,这可能与本研究纳入的样本量少有关。此外,降钙素原水平的升高也从侧面反映机体处于炎症反应过激状态,是机体免疫功能亢进的表现,研究表明脓毒症患者大多可度过早期的全身炎症反应期,后期代偿性抗炎反应引起的免疫瘫痪才是引起脓毒症患者死亡的主要原因^[19],因此降钙素原在一定范围内的升高对机体来说可能并不是一件坏事。

IL-6是一种常见的促炎细胞因子,能够激活机体免疫细胞的增殖分化并提高其免疫清除和免疫防御功能^[20]。有研究表明IL-6与脓毒症患者不良预后存在相关性^[21]。Kellum等^[22]研究发现,当促炎细胞因子IL-6水平与抗炎细胞因子IL-10水平均较高时,脓毒症患者死亡风险大大增加。本研究结果也表明IL-6水平升高是脓毒症患者死亡的独立危险因素($P<0.05$),且随着IL-6水平的升高脓毒

症患者发生死亡的风险增加。

综上所述,住院期间使用CRRT、IL-6水平升高、降钙素原水平降低的脓毒症患者入院28 d内死亡的风险较高。密切观察并动态监测脓毒症患者IL-6、降钙素原、肾功能等的变化有助于早期识别可能发生不良结局的患者,从而及时采取措施提高脓毒症患者的救治成功率。此外,气管插管、机械通气、CRRT、深静脉置管等临床有创干预也是一把双刃剑,在改善患者症状、缓解患者痛苦的同时也是导致患者死亡的潜在危险因素,如何准确评估和把握其平衡点是临床医师需要重点考虑的问题。

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