·临床研究·

肝素结合蛋白联合降钙素原对脓毒症相关急性肾损伤死亡风险的预测价值

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【摘 要】 目的 探讨血清肝素结合蛋白(HBP)联合降钙素原(PCT)对脓毒症相关急性肾损伤(SA-AKI)患者28 d死亡风险的预测价值。**方法** 回顾性分析2020年7月至2022年2月山西白求恩医院急诊科重症监护室(ICU)收治的75例SA-AKI患者的临床资料。根据28 d转归情况将患者分为生存组(51例)和死亡组(24例),比较2组患者HBP、PCT等情况。采用SPSS 26.0统计软件进行数据分析。根据数据类型,分别采用t检验、Mann-Whitney U检验或χ^2检验进行组间比较。采用单因素分析和多因素logistic回归分析SA-AKI患者28 d死亡风险的独立影响因素。绘制森林图比较SA-AKI患者死亡风险的独立影响因素差异。绘制受试者工作特征(ROC)曲线评估SA-AKI患者28 d死亡危险因素的预测价值。**结果** 死亡组和生存组HBP[115.66(96.87,255.20)和95.61(46.82,114.79) ng/mL]、PCT[29.13(26.03,111.53)和14.41(6.62,23.91) ng/mL]、血乳酸[3.90(1.75,6.93)和2.02(1.47,4.08) mmol/L]、急性生理与慢性健康状况评分[25.50(21.25,31.00)和20.00(16.00,26.25)分]、序贯器官衰竭评分[(11.46±3.68)和(8.69±3.50)分]、住院时间[9.00(5.50,19.75)和21.50(15.00,30.00) d]、使用机械通气支持治疗[24(100.%)和35(68.6%)],使用血管收缩性药物[22(91.7%)和32(62.7%)]情况比较,差异均有统计学意义($P<0.05$)。logistic回归分析结果显示,HBP($OR=1.155$,95%CI 1.007~1.325)、PCT($OR=2.698$,95%CI 1.003~7.254)、住院时间($OR=0.379$,95%CI 0.144~0.995)是SA-AKI患者28 d预后的独立影响因素。ROC曲线结果显示,HBP预测的曲线下面积(AUC)为0.755,最佳截断值为65.815 ng/ml,灵敏度为58.3%,特异度为78.4%;PCT预测的AUC为0.871,最佳截断值为20.670 ng/ml,灵敏度为100.0%,特异度为64.7%;两者联合检测的AUC为0.903,最佳截断值为0.222 ng/ml,灵敏度为100.0%,特异度为70.6%。**结论** 血清HBP和PCT水平升高是SA-AKI患者28 d死亡的独立危险因素。血清HBP、PCT水平对SA-AKI患者28 d死亡具有良好的预测价值,两者联合检测预测效能最佳。

【关键词】 肝素结合蛋白;降钙素原;脓毒症;急性肾损伤;预后

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Predictive value of heparin binding protein and procalcitonin for mortality risk in patients with sepsis associated acute kidney injury

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【Abstract】 Objective To investigate the predictive value of serum heparin binding protein (HBP) and procalcitonin (PCT) for 28-day mortality risk in patients with sepsis associated acute kidney injury (SA-AKI). **Methods** A retrospective analysis was performed of the clinical data of 75 SA-AKI patients admitted to the intensive care unit (ICU) of Emergency Department in Shanxi Bethune Hospital from July 2020 to February 2022. They were divided into the survival group ($n=51$) and death group ($n=24$) based on 28-day outcome, and the two groups were compared in HBP, PCT and other clinical data. SPSS statistics 26.0 was used for data analysis. Depending on the data type, t-test, Mann-Whitney U test, or χ^2 test was used for comparison between groups. Univariate analysis and multivariate logistic regression were used to analyze the factors influencing the risk of death at 28 days, and forest plots

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were drawn to compare the independent prognostic factors. Receiver operating characteristic (ROC) curve was drawn to evaluate the predictive value of 28-day death risk factors. **Results** The two groups differed significantly in HBP [115.66 (96.88, 255.20) *vs* 95.61(46.82, 114.79) ng/ml], PCT [29.13(26.03, 111.53) *vs* 14.41(6.62, 23.91) ng/ml], lactic acid [3.90(1.75, 6.93) *vs* 2.02(1.47, 4.08) mmol/L], APACHE Ⅱ [25.50 (21.25, 31.00) *vs* 20.00(16.00, 26.25) points], SOFA [(11.46±3.68) *vs* (8.69±3.50) points], hospital stay [9.00(5.50, 19.75) *vs* 21.50(15.00, 30.00) d], use of mechanical ventilation support [24(100.0%) *vs* 35(68.6%)], and use of vasoconstrictor [22(91.7%) *vs* 32(62.7%)] (P<0.05). Logistic regression analysis showed that HBP (OR= 1.155, 95% CI 1.007-1.325), PCT (OR=2.698, 95% CI 1.003-7.254) and hospital stay (OR= 0.379, 95%CI 0.144-0.995) were independent influencing factors for death at 28 days in the SA-AKI patients. ROC curve analysis showed an area under the curve (AUC) of 0.755 for HBP with an optimal cut-off value of 65.815 ng/ml, a sensitivity of 58.3% and a specificity of 78.4%; an AUC of 0.871 for PCT with an optimal cut-off value of 20.670 ng/ml, a sensitivity of 100.0% and a specificity of 64.7%; and an AUC of 0.903 both with an optimal cut-off value of 0.222 ng/ml, a sensitivity of 100.0% and a specificity of 70.6%. **Conclusion** Elevated serum levels of HBP and PCT were independent risk factors for 28-day death in SA-AKI patients. Serum levels of HBP and PCT have good predictive value for 28-day death in SA-AKI patients, and they predict better in combination than individually.

【Key words】 heparin binding protein; procalcitonin; sepsis; acute kidney injury; prognosis

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急性肾损伤(acute kidney injury,AKI)指短时间内肾脏滤过功能突然减退或丧失[1],脓毒症是导致危重症患者 AKI 的主要原因之一。关于脓毒症相关急性肾损伤(sepsis associated acute kidney injury, SA-AKI)发病机制的最新观点认为,其发生与炎症反应、微循环紊乱及代谢重编程有关[2]。SA-AKI 患者的死亡率高,早期可逆性 AKI 与提高生存率有关[3]。因此早期识别高风险的 SA-AKI 患者,进而及时干预并逆转 AKI 可能有益于提高生存率。肝素结合蛋白(heparin binding protein,HBP)通过增加血管内皮通透性、细胞周期阻滞和促进炎症反应在 SA-AKI 患者中发挥作用[4]。因此,HBP 可能早期诊断 SA-AKI 并预测其死亡率。已有研究证明 HBP 与 SA-AKI 早期诊断有关,但目前尚无 HBP 与 SA-AKI 预后相关的研究。早期 AKI 患者血清中降钙素原(procalcitonin,PCT)水平显著增高,并与病情严重程度相关,表明其可作为早期诊断 AKI 及评估预后的生物标志物[5]。因此,本研究探讨血清 HBP 联合 PCT 对 SA-AKI 患者预后的评估价值,以帮助临床医师早期识别预后不良的高风险 SA-AKI 患者。

1 对象与方法

1.1 研究对象

选取 2020 年 12 月至 2022 年 2 月山西省白求恩医院急诊科重症监护室(intensive care unit,ICU)诊治的 75 例 SA-AKI 患者为研究对象。根据 28 d 预后情况将患者分为生存组(51 例)和死亡组(24 例)。纳入标准:(1)符合《第 3 次脓毒症和脓毒症休克定义国际共识(sepsis-3)》[6]诊断标准;(2)符合 2012 年改善全球肾脏病预后组织制定的 AKI 诊断标准[7];(3)年龄>18 岁;(4)临床资料完整。排除标准:(1)治疗过程中自动放弃出院;(2)存在慢性肾功能不全;(3)入院前 1 周内暴露于肾毒性药物;(4)入院前已接受肾脏替代治疗;(5)各种疾病终末期或临终状态;(6)妊娠期或哺乳期妇女;(7)随访失访;(8)低氧血症;(9)低血容量;(10)水电解质、酸碱平衡紊乱。

1.2 方法

所有患者采集入院 24 h 内的静脉血及动脉血。收集纳入患者的年龄、性别、有无基础疾病等一般资料;器官衰竭个数、ICU 住院时间、平均动脉压、氧合指数、急性生理与慢性健康状况评分(acute physiology and chronic health evaluation Ⅱ, APACHE Ⅱ)、序贯器官衰竭评分(sequential organ failure assessment, SOFA),连续肾脏替代治疗(continuous renal replacement therapy,CRRT)、机械通气、血管收缩性药物的应用;血清 HBP、PCT、血肌酐、尿素氮、肾小球滤过率、血乳酸、血气分析、白细胞计数、中性粒细胞计数及诊断后 28 d 生存情况。以上所有检验指标及评分均为入院 24 h 内的最差值。

1.3 统计学处理

采用 SPSS 26.0 统计软件进行数据分析。正态分布的计量资料以均数±标准差($\bar{x}\pm s$)表示,组间比较采用 t 检验;不符合正态分布的计量资料使用中位数(四分位数间距)[$M(Q_1, Q_3)$]表示,组间比较采用非参数 Mann-Whitney U 检验。计数资料以例数(百分率)表示,组间比较采用 χ^2 检验。采用多因素回归分析 SA-AKI 患者 28 d 预后的影响因素。

采用 GraphPad Prism 绘制森林图直观比较 SA-AKI 患者 28 d 预后的影响因素的差异。绘制受试者工作特征(receiver operating characteristic, ROC)曲线评估各指标对 SA-AKI 患者 28 d 预后的预测价值。$P<0.05$ 为差异有统计学意义。

2 结 果

2.1 2 组患者临床资料比较

SA-AKI 患者 28 d 病死率为 32.0%(24/75)。2 组患者年龄、性别、基础疾病、平均动脉压、使用 CRRT 比率、氧合指数(partial pressure of oxygen/fraction of inspiration oxygen, PaO_2/FiO_2)比较,差异均无统计学意义($P>0.05$)。而 APACHE Ⅱ评分、SOFA 评分、使用机械通气比率、使用血管收缩性药物比率、ICU 住院时间比较,差异有统计学意义($P<0.05$;表 1)。

2.2 2 组患者生化指标比较

2 组患者 HBP、PCT 及乳酸水平差异有统计学意义($P<0.05$);血钾、肌酐、尿素氮、肾小球滤过率、白细胞计数、中性粒细胞计数等生化指标比较,差异均无统计学意义($P>0.05$;表 2)。

2.3 logistic 回归分析患者 28 d 死亡风险的独立影响因素

将单因素分析中所有阳性变量即 HBP、PCT、乳酸、APACHE Ⅱ评分、SOFA 评分、机械通气、血管收缩性药物、ICU 住院时间纳入多因素 logistic 回归方程,结果表明,HBP、PCT 水平及 ICU 住院时间是 SA-AKI 患者 28 d 死亡的独立影响因素(表 3)。

表 1 2 组患者临床资料比较

Table 1 Comparison of baseline data between two groups

Item	Survival group($n=51$)	Death group($n=24$)	$t/Z/\chi^2$	P value
Age(years, $\bar{x}\pm s$)	61.46±13.71	61.12±16.53	−0.088	0.930
Female[n(%)]	32(62.7)	16(66.7)	0.109	0.741
MAP(mmHg, $\bar{x}\pm s$)	88.42±2.74	83.79±4.26	0.034	0.522
APACHE Ⅱ[points, $M(Q_1,Q_3)$]	20.00(16.00,26.25)	25.50(21.25,31.00)	−3.026	0.002
SOFA(points, $\bar{x}\pm s$)	8.69±3.50	11.46±3.68	−3.146	0.002
ICU stay[d, $M(Q_1, Q_3)$]	21.50(15.00,30.00)	9.00(5.50,19.75)	−4.029	0.001
Number of failure organ[n(%)]			7.644	0.054
1	17(33.3)	3(12.5)		
2	17(33.3)	8(33.3)		
3	14(27.5)	7(29.2)		
4	3(5.9)	6(25.0)		
CRRT[n(%)]	16(31.4)	12(50.0)	2.420	0.120
MV[n(%)]	35(68.6)	24(100.0)	9.571	0.002
Vasoconstrictor[n(%)]	32(62.7)	22(91.7)	6.771	0.009
Primary disease[n(%)]	29(56.9)	10(41.7)	1.510	0.219
PaO_2/FiO_2(mmHg, $\bar{x}\pm s$)	237.91±104.21	214.73±92.56	0.930	0.355

MAP: mean arterial pressure; APACHE Ⅱ: acute physiology and chronic health evaluation Ⅱ; SOFA: sequential organ failure assessment; ICU: intensive care unit; CRRT: continuous renal replacement therapy; MV: mechanical ventilation; PaO_2/FiO_2: partial pressure of oxygen/fraction of inspiration oxygen. 1 mmHg = 0.133 kPa.

表 2 2 组患者生化指标比较

Table 2 Comparison of biochemical indicators between two groups [$M(Q_1, Q_3)$]

Item	Survival group($n=51$)	Death group($n=24$)	Z	P value
HBP(ng/ml)	95.61(46.82,114.79)	115.66(96.87,255.20)	−3.544	0.001
PCT(ng/ml)	14.41(6.62,23.91)	29.13(26.03,111.53)	−5.151	0.001
K^+(mmol/L)	4.21(3.77,4.74)	4.14(3.48,4.54)	−0.993	0.321
SCr(μmol/L)	205.35(152.50,272.40)	194.05(143.90,346.75)	−0.363	0.716
BUN(mmol/L)	16.00(10.83,26.56)	18.70(11.90,25.98)	−0.801	0.423
eGFR(mL/min)	27.20(17.45,36.60)	27.84(13.46,38.70)	−0.125	0.901
Lac(mmol/L)	2.02(1.47,4.08)	3.90(1.75,6.93)	−2.437	0.015
WBC($\times10^9$/L)	10.30(7.90,14.15)	11.85(5.50,20.33)	−0.369	0.712
NEUT($\times10^9$/L)	9.63(7.00,13.10)	10.64(4.73,19.38)	−0.170	0.865

HBP: heparin binding protein; PCT: procalcitonin; SCr: serum creatinine; BUN: blood urea nitrogen; eGFR: estimated glomerular filtration rate; Lac: lactic acid; WBC: white blood cells; NEUT: neutrophile granulocyte.

表3 患者28 d死亡风险多因素logistic回归分析

Table 3 Multivariate logistic regression analysis of 28 d death risk

Factor	*B*	*S*	*W*	*P* value	*OR*	95%*CI*
HBP	0.144	0.070	4.259	0.039	1.155	1.007-1.325
PCT	0.992	0.505	3.866	0.049	2.698	1.003-7.254
Lac	2.064	1.181	3.055	0.081	7.877	0.778-79.728
APACHE Ⅱ	-0.517	0.401	1.667	0.197	0.596	0.272-1.307
SOFA	1.298	0.786	2.727	0.099	3.663	0.785-17.098
MV	21.501	5285.069	0.001	0.997	2.180×10^{9}	0.001-
Vasoconstrictor	21.054	58.023	0.132	0.717	1.390×10^{9}	0.001-
ICU stay	-0.970	0.492	3.881	0.049	0.379	0.144-0.995

HBP: heparin binding protein; PCT: procalcitonin; Lac: lactic acid; APACHE Ⅱ: acute physiology and chronic health evaluation Ⅱ; SOFA: sequential organ failure assessment; MV: mechanical ventilation; ICU: intensive care unit.

2.4 SA-AKI患者28 d死亡风险的独立影响因素比较

HBP水平每增加1,死亡风险增加0.155倍;PCT水平每增加1,死亡风险增加1.698倍(图1)。

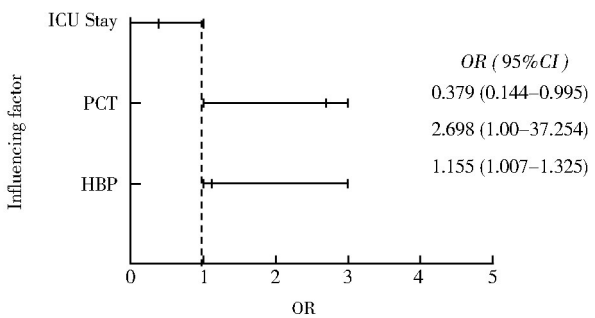

图1 患者28 d死亡风险独立影响因素的森林图

Figure 1 Forest plot of independent factors influencing 28 d risk of death

ICU: intensive care unit; PCT: procalcitonin; HBP: heparin binding protein.

2.5 ROC曲线分析患者28 d死亡风险

ROC曲线分析SA-AKI患者的预后情况,HBP预测的ROC曲线下面积(area under the curve, AUC)为0.755,最佳截断值为65.815 ng/ml,灵敏度为58.3%,特异度为78.4%(约登指数为0.368,95%*CI* 0.640~0.870,$P<0.01$);PCT预测的AUC为0.871,最佳截断值为20.670 ng/ml,灵敏度为100.0%,特异度为64.7%(约登指数为0.647,95%*CI* 0.793~0.948,$P<0.01$);HBP联合PCT预测的AUC为0.903,最佳截断值为0.222 ng/ml,灵敏度为100.0%,特异度为70.6%(约登指数为0.706,95%*CI* 0.838~0.968,$P<0.01$;图2)。

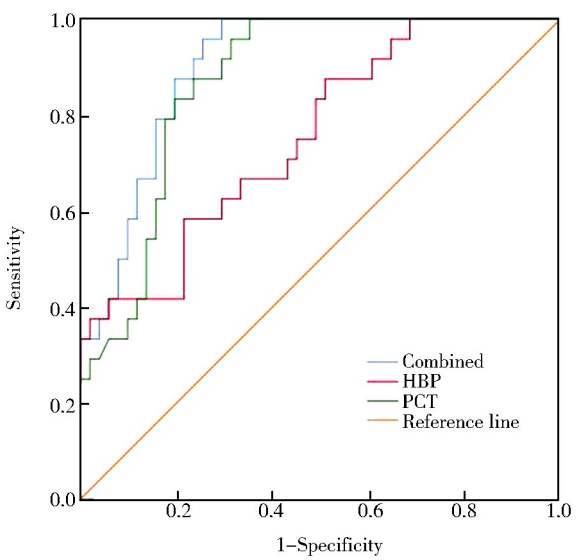

图2 HBP、PCT及两者联合评估患者28 d死亡的ROC曲线

Figure 2 ROC curve of HBP, PCT and their combined evaluation of 28 d death

HBP: heparin binding protein; PCT: procalcitonin; ROC: receiver operating characteristic.

3 讨 论

脓毒症患者可因感染引起全身瀑布式炎症反应,进一步引起脓毒性休克及器官功能衰竭。肾脏是脓毒症患者最易累及的器官之一,脓毒症患者发展至SA-AKI后可使死亡率增加6~8倍[8]。Chua等[9]通过对207例患者预后的研究发现,SA-AKI患者病死率为27.1%。本研究中75例患者病死率为32.0%(24/75),与上述研究结果相近。由于SA-AKI死亡率较高,寻找适合的生物标志物早期识别SA-AKI患者不良预后的风险并指导临床医师及时干预显得尤为重要。

目前研究证明HBP可以早期诊断SA-AKI[10-12],但是关于HBP对SA-AKI预后的预测价值研究很少。Fisher等[13]对296例脓毒性休克患者进行前瞻性研究,其中SA-AKI患者225例,研究发现使用>5 g/L HBP刺激时,白细胞介素-6明显增高,提示血浆HBP升高与SA-AKI发生有关,HBP可能参与了这一过程。高翔等[12]研究入选

了 96 例脓毒症患者,其中 SA-AKI 患者 58 例,该研究发现血浆 HBP 对 SA-AKI 患者 28 d 预后的 AUC 为 0.817。本研究中 75 例 SA-AKI 患者预后的分析结果显示,HBP 是 SA-AKI 死亡风险的独立危险因素。ROC 曲线结果显示,HBP 预测 SA-AKI 患者死亡风险的 AUC 为 0.755,与上述研究结果相似。本研究中 HBP 预测 SA-AKI 患者死亡风险的特异度较高,为 78.4%,灵敏度为 58.3%,而 PCT 被公认为诊断脓毒症最常用的生物标志物,因此推测 HBP 与 PCT 联合检测可能会提高对 SA-AKI 患者预后的预测能力。

高水平的 PCT 是脓毒症引起的器官功能障碍和 AKI 的风险预测因子,并且与患者的预后呈负相关[14]。梁维等[15]对 98 例脓毒症患者进行回顾性分析,发现 PCT 预测不良预后的 AUC 为 0.81。本研究中死亡组住院时长短于生存组住院时长,多因素分析显示住院时长是 SA-AKI 患者死亡的保护因素,其原因在于本研究中 SA-AKI 患者住院时长本质上是患者入院后的生存时间。

本研究中机械通气及血管活性药物使用率的 *OR* 值与 95%*CI* 的上限值过大,原因可能是样本量过少及数据间的混杂因素导致这两个变量与患者 28 d 预后结局的关联度过高,造成了较大的误差。因此需要更大的样本量来验证机械通气及血管活动药物与 SA-AKI 患者 28 d 预后结局的关系。

综上所述,血清 HBP、PCT 水平增高提示 SA-AKI 患者病情较重及死亡风险高,两者联合检测能够有效预测 SA-AKI 患者 28 d 死亡风险。本研究的局限性在于是单中心、小样本的回顾性研究,很难控制偏倚及干扰因素,且仅随访了患者短期存活情况,研究结论可能与其他研究有不同之处。因此尚需大规模、多中心的前瞻性临床试验来进一步评价 HBP 及 PCT 的应用价值。

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