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·短篇论著·

脓毒症急性肾损伤患者早期肾功能恢复的影响因素分析

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［摘要］ **目的**　分析脓毒症诱导的急性肾损伤（sepsis-associated acute kidney injury, SA-AKI）患者肾功能早期恢复的影响因素。**方法**　回顾性分析2021年1月至2022年12月在复旦大学附属中山医院重症医学科治疗的86例同时符合脓毒症3.0诊断标准和AKI诊断标准的SA-AKI患者。根据是否在发病后7 d内恢复肾功能，将患者分为恢复组和未恢复组。比较两组患者的临床资料和实验室检查结果。采用单因素和多因素logistic回归分析评估影响SA-AKI患者肾功能恢复的危险因素，使用ROC曲线评估各因素对SA-AKI早期肾功能恢复的预测价值。**结果**　SA-AKI患者肾功能恢复37例（43.02%）。与恢复组相比，未恢复组患者肾脏替代治疗率、住院死亡率和入院后28 d死亡率均更高（$P<0.001$）。多因素logistic回归分析显示，年龄、APACHE Ⅱ评分、尿量、尿中性粒细胞明胶酶相关脂质运载蛋白（neutrophil gelatinase-associated lipocalin, NGAL）、去甲肾上腺素剂量是影响SA-AKI患者肾功能恢复的独立相关因素（$P<0.05$），回归模型logit(P)＝－4.091＋0.001×尿NGAL－0.001×尿量＋0.040×年龄＋0.073×APACHE Ⅱ评分＋1.906×去甲肾上腺素剂量。该模型预测SA-AKI早期肾功能恢复的AUC为0.823，灵敏度为73.5%、特异度为81.1%。**结论**　年龄、APACHE Ⅱ评分、尿量、尿NGAL、去甲肾上腺素剂量影响SA-AKI患者肾功能早期恢复，可联合用于评估SA-AKI患者早期肾功能能否恢复。

［关键词］ 脓毒症；急性肾损伤；肾功能恢复；影响因素
［中图分类号］ R 692　　［文献标志码］ A

Analysis of influence factors of early renal function recovery in patients with sepsis-associated acute kidney injury

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［**Abstract**］ **Objective**　To analyze the factors influencing the early recovery of renal function in patients with sepsis-associated acute kidney injury (SA-AKI). **Methods**　A retrospective analysis was conducted on 86 SA-AKI patients treated in the Intensive Care Unit at Zhongshan Hospital, Fudan University from January 2021 to December 2022, who met both the Sepsis 3.0 diagnostic criteria and the AKI diagnostic standards. Patients were divided into a recovery group and a non-recovery group based on whether their renal function recovered within 7 days after AKI onset. Clinical data and laboratory tests of patients were compared between the two groups. Univariate and multivariate logistic analyses were used to identify risk factors affecting renal function recovery in SA-AKI patients, and ROC curve was utilized to evaluate the predictive value of these factors for early renal function recovery in SA-AKI patients. **Results**　The renal function of 37 (43.02%) patients recoveried. Compared with the recovery group, the renal replacement therapy rate, in-hospital mortality and 28-day mortality of patients in the non-recovery group were higher ($P<0.001$). The multivariate logistic analysis showed that age, APACHE Ⅱ score, urine output, urine neutrophil gelatinase-associated lipocalin (NGAL), and norepinephrine dose were independent related factors affecting renal function recovery in SA-AKI patients ($P<0.05$). The final model logit(P)＝－4.091＋0.001×urine NGAL－0.001×urine volume＋0.040×age＋0.073×APACHE Ⅱ score＋1.906×norepinephrine dose. The AUC of model predicting early SA-AKI recovery was 0.823, with 73.5% of sensitivity, and 81.1% of specificity. **Conclusions**　In SA-AKI patients, age, APACHE Ⅱ score, urine output, urine NGAL, and the dose of norepinephrine independently affect early renal function recovery, and the combined assessment of these indicators has predictive value for the early renal recovery in these patients.

［**Key Words**］ sepsis; acute kidney injury; renal function recovery; influence factor

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全球范围内，每年约有4 890万人罹患脓毒症，脓毒症相关死亡占全球总死亡数的19.7%[1]。随着人口老龄化的加剧和抗药性感染发生率的升高，脓毒症的发病率有上升趋势。65岁及以上人群中，脓毒症的发生率较其他年龄段高出20.4%[2]。

急性肾损伤（acute kidney injury, AKI）在住院患者中的发病率为3.2%～20%[3]。脓毒症是AKI的主要病因之一，40%～50%的脓毒症患者会出现不同程度的AKI，而AKI使脓毒症患者院内死亡率升高6～8倍[4]。而且，脓毒症相关AKI（sepsis-associated acute kidney injury, SA-AKI）较其他相关AKI导致的院内死亡率更高，患者住院时间更长[5]。10%～30%的AKI患者出院后仍需透析治疗[6]，同时再住院风险较高。因此，通过早期识别肾功能难以恢复的SA-AKI患者，进而及时干预，可能改善其预后。本研究拟通过回顾性分析脓毒症患者相关临床及实验室资料，探讨影响SA-AKI患者肾功能早期恢复的相关因素，以期为SA-AKI高危患者早期识别和预后判断提供参考。

1 资料与方法

1.1 研究对象 回顾性选择复旦大学附属中山医院重症医学科2021年1月至2022年12月收治的2 329例患者，纳入同时符合脓毒症3.0诊断标准和AKI诊断标准的患者86例。AKI依据以下任一条诊断：48 h内肾功能急速恶化，血肌酐升高超过26.5 μmol/L或增加超过50%；尿量减少至0.5 mL•kg^{-1}•h^{-1}，持续6 h或以上[7]。排除标准：（1）有慢性肾功能衰竭病史；（2）接受过肾脏移植手术；（3）患有肾脏良性或恶性肿瘤；（4）患有肾脏血管性疾病；（5）AKI由明确的非脓毒症因素引起；（6）临床或实验室检查数据缺失。根据肾功能恢复情况，将患者分为AKI恢复组和AKI未恢复组。

1.2 观察指标 （1）临床指标：采集患者的年龄、性别、体质量指数（body mass index, BMI）、血压、使用血管活性药物的剂量、24 h尿量；（2）结局指标：是否采用肾脏替代治疗、AKI恢复与否、入住ICU时间、总住院时间以及入院后28 d内死亡率等；（3）实验室指标：收集入ICU 24 h内血常规、肝功能、肾功能指标，心肌酶谱，降钙素原、血肌酐水平，尿中性粒细胞明胶酶相关脂质运载蛋白（neutrophil gelatinase-associated lipocalin，NGAL）结果。AKI恢复定义为在发病后7 d内，血清肌酐水平降至发病前基线值的150%以内，且未出现超过6 h的少尿（尿量＜5 mL • kg^{-1} • h^{-1}）[8]。

1.3 统计学处理 使用SPSS 20.0软件进行数据分析。符合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；不符合正态分布的计量资料以$M(P_{25}, P_{75})$表示，两组间比较采用Mann-Whitney U检验。计数资料以n(%)表示，组间比较采用卡方检验。采用单因素和多因素的logistic回归分析评估肾功能恢复的影响因素，并建立回归模型。绘制ROC曲线，计算回归模型预测肾功能恢复的曲线下面积（AUC）及灵敏度和特异度，应用R 4.2.3软件对AUC进行Delong检验。检验水准（α）为0.05。

2 结 果

2.1 两组患者基线资料及临床结局比较 86例患者中，37例（43.02%）肾功能恢复。结果（表1）显示：与恢复组相比，未恢复组患者年龄更大、急性生理学与慢性健康状况评估系统Ⅱ（Acute Physiology and Chronic Health Evaluation Ⅱ, APACHE Ⅱ）评分更高、使用去甲肾上腺素的剂量更大、平均动脉压更低，尿量更少、尿比重更大、尿NGAL水平更高，基线肌酐、心肌肌钙蛋白T水平更高（P＜0.05）。未恢复组患者接受肾脏替代治疗的比例、住院死亡率及28 d内死亡率均高于恢复组（P＜0.001）。

2.2 肾功能恢复影响因素分析 单因素logistic回归分析（表2）显示：年龄、APACHE Ⅱ评分、去甲肾上腺素剂量、平均动脉压、尿量、尿NGAL、基线肌酐与SA-AKI患者早期肾功能恢复相关（P＜0.05）。将单因素分析中差异有统计学意义的变量纳入多因素logistic逐步回归分析，结果（表2）显示：年龄、APACHE Ⅱ评分、去甲肾

上腺素剂量、尿量、尿NGAL是SA-AKI患者早期肾功能恢复的独立预测因素（$P<0.05$）。回归模型 logit(P)＝－4.091＋0.001×尿NGAL－0.001×尿量＋0.040×年龄＋0.073×APACHE Ⅱ评分＋1.906×去甲肾上腺素剂量。

表1　两组患者基线资料和临床结局比较

Table 1　Comparison of baseline data and clinical outcomes between the two groups

Index	Recovery group (n＝37)	Non-recovery group (n＝49)	$\chi^2/t/z$ value	P value
Age/year	68.35(63.09,73.61)	75.71(72.41,79.02)	－2.186	0.029
Male n(%)	24(64.86)	35(71.43)	0.422	0.516
BMI/(kg•m^{-2})	22.37±3.00	23.06±3.31	－0.998	0.321
Comorbidity n(%)	22(59.45)	37(75.51)	1.831	0.176
Hypertension	17(45.95)	29(59.18)	1.485	0.223
Diabetes	8(21.62)	9(18.37)	0.141	0.708
CHD	6(16.22)	9(18.37)	0.068	0.795
APACHE Ⅱ score	15.81±6.17	19.78±8.40	－2.003	0.018
NE/(μg•kg^{-1}•min^{-1})	0.16(0.07,0.25)	0.39(0.25,0.55)	－2.862	0.004
MAP/mmHg	83.49±14.69	77.37±11.56	2.163	0.033
Urine output/mL	1361.08(1066.53,1655.64)	734.06(549.94,918.18)	－3.598	＜0.001
Urine osmolality/(mOsm•kg^{-1})	372.50(318.48,426.52)	333.68(290.27,377.08)	－1.300	0.194
Urine specific gravity	1.020±0.01	1.019±0.01	0.431	0.668
Urinary NGAL/(μg•L^{-1})	482.63(265.22,700.04)	925.22(758.68,1262.25)	－3.758	＜0.001
Creatinine/(mmol•L^{-1})	75.51(70.26,85.20)	80.54(73.84,84.12)	－1.358	0.046
WBC/(×10^9•L^{-1})	14.19(11.42,16.96)	13.21(10.00,16.42)	－1.100	0.271
Procalcitonin/(ng•mL^{-1})	19.67(11.13,28.20)	30.59(22.40,46.77)	－1.344	0.179
Hemoglobin/(g•L^{-1})	90.59±19.56	89.06±29.37	0.273	0.785
Platelet count/(×10^9•L^{-1})	132.00(122.21,194.82)	128.00(107.64,154.64)	－0.912	0.362
Total bilirubin/(mmol•L^{-1})	30.19(22.14,51.14)	39.80(29.04,79.33)	－0.201	0.841
Direct bilirubin/(mmol•L^{-1})	21.19(14.78,37.81)	30.58(21.73,58.39)	－0.100	0.920
Albumin/(g•L^{-1})	29.00(27.93,31.74)	31.00(30.01,32.89)	－1.574	0.115
cTnT/(ng•mL^{-1})	0.031(0.006,0.141)	0.081(0.010,2.825)	－3.760	0.001
D-Dimer/(mg•L^{-1})	8.05(6.35,11.62)	9.61(7.91,13.44)	－0.650	0.516
NT-proBNP/(pg•mL^{-1})	3 183.89(1 493.06,4 874.72)	4 404.70(2 805.39,6 004.01)	－1.391	0.164
PT/s	16.38(15.49,17.49)	19.07(17.42,23.13)	－1.012	0.312
APTT/s	41.37(37.77,46.40)	48.64(44.39,61.80)	－1.527	0.127
MV duration/d	4.83(3.40,7.90)	9.76(6.88,22.76)	－1.743	0.081
RRT n(%)	7(18.92)	35(71.43)	23.263	＜0.001
Length of ICU stay/d	9.03(6.65,11.40)	19.02(10.90,27.14)	－1.788	0.074
In-hospital mortality n(%)	2(5.41)	34(69.39)	35.460	＜0.001
28-day mortality n(%)	1(2.70)	23(46.94)	20.504	＜0.001

BMI：body mass index; CHD: coronary heart disease; RRT: renal replacement therapy; APACHE Ⅱ：Acute Physiology and Chronic Health Evaluation Ⅱ；NE: norepinephrine; MAP: mean arterial pressure; NGAL: neutrophil gelatinase-associated lipocalin; WBC: white blood cell; cTnT: cardiac troponin T; NT-proBNP: N-terminal pro-B-type natriuretic peptide; PT: prothrombin time; APTT: activated partial thromboplastin time; MV: mechanical ventilation.

2.3　回归模型对SA-AKI患者肾功能恢复预测价值　结果（表3、图1）显示：NGAL（AUC 0.737）、尿量（AUC 0.728）、年龄（AUC 0.638）、APACHE Ⅱ评分（AUC 0.643）、去甲肾上腺素剂量（AUC 0.677）对SA-AKI肾功能恢复的预测价值中等；回归模型预测SA-AKI患者肾功能恢复的AUC为0.823，灵敏度为73.5%、特异度为81.1%（$P<0.001$），预测价值高于任何单一指标。

表 2 SA-AKI 患者早期肾功能恢复影响因素的 logistic 回归分析

Table 2 Logistic regression analysis of influence factors for early renal function recovery in SA-AKI patients

Variable	Univariate analysis		Multivariate analysis	
	OR(95%CI)	*P* value	OR(95%CI)	*P* value
Age	1.042(1.007-1.078)	0.019	1.043(1.001-1.088)	0.047
APACHE Ⅱ score	1.099(1.012-1.193)	0.025	1.103(1.008-1.208)	0.034
NE	6.208(1.202-32.064)	0.029	6.599(1.138-38.267)	0.035
MAP	0.963(0.930-0.999)	0.041	0.976(0.935-1.019)	0.275
Urine output	0.999(0.998-1.000)	0.001	0.999(0.998-1.001)	0.025
Urine osmolality	0.999(0.995-1.004)	0.697		
Urine specific gravity	0.445(0.001-4.877)	0.384		
Urinary NGAL	1.001(1.000-1.002)	0.009	1.001(0.999-1.002)	0.038
Creatinine	1.015(0.997-1.033)	0.044	1.000(0.975-1.026)	0.334
WBC	0.990(0.949-1.034)	0.653		
Procalcitonin	1.013(0.999-1.028)	0.070		
Hemoglobin	0.998(0.981-1.014)	0.782		
Platelet count	0.997(0.992-1.002)	0.190		
Total bilirubin	1.004(0.997-1.011)	0.281		
Direct bilirubin	1.006(0.996-1.015)	0.251		
Albumin	1.061(0.975-1.154)	0.171		
cTnT	10.380(0.627-171.884)	0.102		
D-Dimer	1.023(0.972-1.076)	0.386		
NT-proBNP	1.045(0.980-1.114)	0.182		
PT	1.077(0.995-1.166)	0.066		
APTT	1.024(0.998-1.052)	0.070		

APACHE Ⅱ：Acute Physiology and Chronic Health Evaluation Ⅱ；NE: norepinephrine; MAP: mean arterial pressure; NGAL: neutrophil gelatinase-associated lipocalin; WBC: white blood cell; cTnT: cardiac troponin T; NT-proBNP: N-terminal pro-B-type natriuretic peptide; PT: prothrombin time; APTT: activated partial thromboplastin time.

表 3 独立相关因素预测 SA-AKI 患者肾功能恢复的价值

Table 3 The values of independent predictors for renal function recovery in SA-AKI patients

Index	AUC	Standard error	95%CI	Cut-off value	Sensitivity/%	Specificity/%	*P* value
Age	0.638	0.061	0.519-0.758	72 yeas	63.3	54.1	0.029
APACHE Ⅱ score	0.643	0.059	0.527-0.759	21	40.8	81.1	0.023
NE dose	0.677	0.059	0.561-0.793	0.315 μg•kg^{-1}•min^{-1}	36.7	83.8	0.005
Urinary NGAL	0.737	0.054	0.632-0.843	567.25 μg/L	61.2	64.9	＜0.001
Urine output	0.728	0.054	0.621-0.834	785.00 mL	65.3	78.4	＜0.001
Logistic model	0.823	0.046	0.733-0.914		73.5	81.1	＜0.001

APACHE Ⅱ：Acute Physiology and Chronic Health Evaluation Ⅱ；NE: norepinephrine; NGAL: neutrophil gelatinase-associated lipocalin.

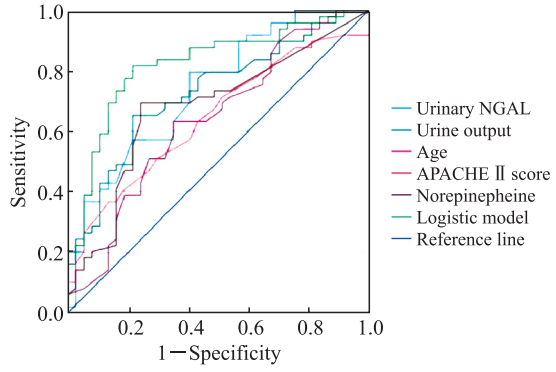

图 1 ROC 分析相关因素预测 SA-AKI 患者肾功能恢复的价值

Figure 1 ROC analysis of related factors predicting renal function recovery in SA-AKI patients

3 讨 论

肾脏血流量约占心脏总输出量的 20%[9]。肾脏高氧消耗和高血流的特点使其在脓毒症发生后更易受累[10]。SA-AKI 患者转变为慢性肾病的风险较大，部分需要接受长期的肾脏替代治疗[11]。AKI 患者中，约 7.5% 须进行长期透析治疗，30%～70% 会进展为慢性肾损伤、终末期肾病等[12]。AKI 患者的长期预后与出院时的肾功能恢复状况密切相关[11]。

目前尚无统一的肾功能恢复定义，而且根据不同的研究对象和肾损伤恢复定义，肾功能未完

全恢复的发生率为11%～53%[13-15]。本研究参考了2017年美国急性透析质量倡议（Acute Dialysis Quality Initiative, ADQI）工作组标准，将肾功能恢复定义为在发病7 d内血肌酐水平下降至基线1.5倍以内[16]。多种临床指标影响AKI患者肾功能的恢复，包括年龄、遗传因素、合并症、多器官功能障碍等。细胞周期阻滞、炎症细胞渗透及纤维化可能是AKI进展为慢性肾功能衰竭的机制[17]。

临床上，血肌酐是诊断AKI及评估AKI后肾功能恢复的主要指标。但是，肌酐变化常滞后，其首次显著变化一般出现在AKI发生后24～48 h；并且只有当肾小球滤过率降低超过其基线值的50%时，肌酐水平才会显著上升[18]。NGAL对肾功能变化高度敏感，主要在肾脏近端小管被重吸收[19]。Srisawat等[20]认为，尿液中的NGAL与肾细胞的损伤相关，监测NGAL浓度有助于预测肾脏恢复情况。本研究显示，尿NGAL降低是独立预测SA-AKI患者早期肾功能恢复的指标。尿量作为直观反映肾功能的指标，能有效预测AKI的发生[21]。本研究结果与之一致，肾脏储备功能与年龄相关，随着年龄增加，肾小球储备减少[22]。急性疾病的严重程度[23]与血流动力学[24]也影响肾功能恢复过程。本研究显示，尿量、年龄、APACHE Ⅱ评分和去甲肾上腺素剂量也独立影响SA-AKI早期肾功能恢复。

本研究基于上述独立影响因素，进一步构建了SA-AKI肾功能恢复预测模型，模型AUC为0.823。Srisawat等[25]仅用NGAL预测社区获得性肺炎后AKI患者肾功能恢复的AUC为0.74。本研究NGAL预测SA-AKI患者肾功能恢复的AUC为0.737，低于预测模型。Stanski等的研究[26]中，C-C趋化因子配体3、颗粒酶B、热休克蛋白70 1B、IL-8和基质金属蛋白酶8等联合预测脓毒症休克伴严重AKI患儿肾功能恢复的AUC为0.83。该研究应用指标获取难于本研究，临床可操作性较差。Zhao等[27]的预测模型中包含更多的临床和实验室指标，临床实用性欠佳。

本研究存在一定的局限性：（1）数据来源于单中心，缺乏外部验证，而不同地区医疗水平、患者人群和资源配置存在差异，可能导致研究结果的外推性受限；（2）回顾性研究可能导致结果偏倚；（3）样本量较小可能影响重要效应或关系的发现，同时不利于混杂因素的准确识别。

综上所述，本研究构建的模型对SA-AKI患者早期肾功能恢复有较高预测价值，且临床可操作性较强。临床可根据年龄、APACHE Ⅱ评分、尿量、尿NGAL、去甲肾上腺素剂量，及时调整治疗方案，进而改善SA-AKI患者预后。未来须进行更大样本量、更长随访时间的前瞻性研究来验证本研究结论。

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