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脓毒症合并急性肾损伤患者尿液 NGAL 水平与肾动脉阻力指数、APACHE II 评分及 28 d 病死率的关系*

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摘要 目的:研究脓毒症合并急性肾损伤(AKI)患者尿液中性粒细胞明胶酶相关脂质运载蛋白(NGAL)水平与肾动脉阻力指数(RRI)、急性生理学及慢性健康状况评分系统 II (APACHE II) 评分及 28 d 病死率的关系。**方法:**选取 2017 年 2 月~2019 年 12 月期间我院收治的脓毒症患者 251 例纳入研究,将其按照是否发生 AKI 分为 AKI 组 116 例和非 AKI 组 135 例。检测并比较两组尿液 NGAL 水平、RRI、APACHE II 评分。采用 Pearson 相关性分析尿液 NGAL 水平与 RRI、APACHE II 评分的关系。此外,将 AKI 组患者按照随访 28d 时是否死亡分为死亡组 32 例和存活组 84 例,比较两组尿液 NGAL 水平、基线资料、序贯性器官功能衰竭(SOFA)评分以及实验室指标,通过多因素 Logistic 回归分析脓毒症合并 AKI 患者 28 d 死亡率与相关因素的关系。**结果:**AKI 组尿液 NGAL 水平、RRI、APACHE II 评分均明显高于非 AKI 组(均 $P<0.05$)。经 Pearson 相关性分析表明:尿液 NGAL 水平与 RRI、APACHE II 评分均呈正相关(均 $P<0.05$)。死亡组 AKI 分期 2~3 期人数占比高于存活组,且 SOFA 评分、APACHE II 评分以及尿液 NGAL、尿肾损伤分子-1(Kim-1)水平均高于存活组,而尿胱抑素 C(CysC)水平低于存活组(均 $P<0.05$)。经多因素 Logistic 回归分析发现:AKI 分期 2~3 期、SOFA 评分、APACHE II 评分、尿液 NGAL 以及尿 Kim-1 均是脓毒症合并 AKI 患者 28 d 死亡的危险因素,而尿 CysC 为其保护因素(均 $P<0.05$)。**结论:**尿液 NGAL 在脓毒症合并 AKI 患者中明显高表达,且和 RRI、APACHE II 评分及 28 d 病死率密切相关。

关键词:脓毒症;急性肾损伤;中性粒细胞明胶酶相关脂质运载蛋白;肾动脉阻力指数;APACHE II 评分;28d 病死率

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Relationship between Urine NGAL Levels and Renal Artery Resistance Index, APACHE II Score and 28 d Mortality in Patients with Sepsis Complicated with Acute Kidney Injury*

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ABSTRACT Objective: To study the relationship between urine neutrophil gelatinase-associated lipid carrier protein (NGAL) levels and renal artery resistance index (RRI), Acute physiology and chronic health evaluation system II (APACHE II) score and 28 d mortality in patients with sepsis complicated with acute kidney injury (AKI). **Methods:** 251 patients with sepsis admitted to our hospital from February 2017 to December 2019 were included in the study, and divided into 116 patients in the AKI group and 135 patients in the non AKI group according to whether AKI had occurred. The two groups of urine NGAL levels, RRI, APACHE II score were tested and compared. Pearson correlation analysis was used to analyze the relationship between urine NGAL level and RRI, APACHE II score. In addition, patients in the AKI group were divided into the death group with 32 cases and the survival group with 84 cases according to whether they died at 28 d follow-up. Urine NGAL levels, baseline data and sequential organ failure (SOFA) scores and laboratory indicators were compared between the two groups, and the relationship between 28 d mortality and related factors in patients with sepsis complicated with AKI was analyzed by multivariate Logistic regression. **Results:** The urine NGAL level, RRI, APACHE II score in AKI group were significantly higher than those in non AKI group (all $P<0.05$). The Pearson correlation analysis showed that urine NGAL levels and RRI, APACHE II scores were positively correlated(all $P<0.05$). The proportion of patients with AKI stage 2~3 in death group was higher than that in survival group, and SOFA score, APACHE II score, urine NGAL and urinary kidney injury molecule - 1 (Kim-1) levels were higher than those in survival group, and urinary bladder inhibition C(CysC) level was lower than that in survival group(all $P<0.05$). Multivariate Logistic regression analysis showed that AKI stage 2~3, SOFA score, APACHE II score, urine NGAL and urine Kim-1 were the risk

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factors of 28 d death in patients with sepsis complicated with AKI, while urinary CysC was the protective factor (all $P < 0.05$). **Conclusion:** Urine NGAL is highly expressed in patients with sepsis complicated with AKI, and it is closely related to RRI, APACHE II score and 28d mortality.

Key words: Sepsis; Acute kidney injury; Neutrophil gelatinase-associated lipid carrier protein; Renal artery resistance index; APACHE II score; 28 d mortality

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前言

脓毒症属于临床上较为常见的一种全身性危急重症,往往合并多系统脏器的功能衰竭,其中并发急性肾损伤(AKI)的几率高达30%~50%,具有极高的病死率^[1,2]。由此可见,对AKI的早期准确诊断尤为重要,可为临床治疗方案的制定提供指导,继而最大程度上减缓AKI的进展,从而降低病死率^[3,4]。中性粒细胞明胶酶相关脂质运载蛋白(NGAL)属于载脂蛋白家族成员之一,其在生理状态下表达于肾脏组织,而当肾功能遭受损害时,NGAL的表达异常升高,可有效反映早期肾损伤情况^[5,6]。肾动脉阻力指数(RRI)是临床上广泛用以反映肾血流灌注的重要指标,可作为肾功能恶化的有效标志物^[7,8]。急性生理学及慢性健康状况评分系统II(APACHE II)是国内外所公认的最权威的危急重症患者病情评估系统,在病情判断以及预后预测方面起着至关重要的作用^[9]。鉴于此,本文通过研究脓毒症合并AKI患者尿液NGAL水平与RRI、APACHE II评分及28 d病死率的关系,旨在为临床医治此类疾病提供相应的数据支持,现作以下报道。

1 对象与方法

1.1 一般资料

选取2017年2月~2019年12月期间我院收治的脓毒症患者251例纳入研究,将其按照是否发生AKI分作AKI组116例和非AKI组135例。其中AKI组男性65例,女性51例;年龄34~78岁,平均(52.39±5.03)岁。非AKI组男性79例,女性56例;年龄33~79岁,平均(52.51±5.05)岁。两组一般资料对比无明显差异($P > 0.05$),具有可比性。纳入标准:(1)所有入选对象均符合2012国际严重脓毒症及脓毒性休克诊疗指南的相关诊断标准^[10];(2)年龄≥20岁;(3)AKI组患者符合改善全球肾脏病预后组织的AKI诊断标准^[11];(4)临床资料完整。排除标准:(1)入院后24 h内死亡者;(2)妊娠期或哺乳期女性;(3)既往接受肾移植手术或慢性肾功能不全者;(4)肾小球肾炎、间质性肾炎等原因引起的AKI患者;(5)神志异常或合并神经系统疾病者。本研究经我院伦理委员会批准,患者或其家属知情同意。

1.2 方法

(1)尿液相关指标检测:于患者入院当天采集所有患者的尿液,以3000 r/min离心处理,获取上清液保存在-80℃冰箱中备用。采用酶联免疫吸附法检测尿液NGAL、尿肾损伤分子-1(Kim-1)水平,具体操作严格按照试剂盒(购自上海基免生物科技有限公司)说明书完成。尿胱抑素C(CysC)水平采用免疫比浊法检测,具体操作严格按照试剂盒(购自美国Abcam公司)

说明书完成。(2)基本资料采集:于患者入院当天,采用医院自制的基本资料调查表收集患者的临床资料,主要内容包括年龄、性别、序贯性器官功能衰竭(SOFA)评分^[12]、APACHE II评分、AKI分期。(3)RRI检测:所有患者禁食8h,且在检查前1 d口服适量的缓泻药。采用迈瑞M6超声仪检测,探头频率为3.5~5.0 MHz,所有检查均由医院同一名经验丰富的医师独立完成。检查时患者均取仰卧位,至少检测双肾上极、中部以及下极等部位,待动脉彩色血流信号满意时,告知患者屏息,测定肾叶间动脉收缩峰值流速(PV)以及舒张末期流速(EDV),计算 $RRI = (PV - EDV) / PV$ 。

1.3 观察指标

对比两组尿液NGAL水平、RRI、APACHE II评分,分析尿液NGAL水平与RRI、APACHE II评分的相关性,对比死亡组与存活组尿液NGAL水平、基线资料、SOFA评分以及实验室指标,分析脓毒症合并AKI患者28 d死亡的影响因素。其中APACHE II评分标准如下^[13]:主要包括年龄评分(6分);急性生理学评分:①体温;②心率;③血压;④氧分压;⑤动脉血PH;⑥呼吸频率;⑦血清肌酐;⑧血清钾;⑨血清钠;⑩红细胞压积以及白细胞计数等生理指标,共44分;慢性健康状况评分:有无慢性严重器官系统功能不全或免疫损害(5分),总分55分。

1.4 统计学处理

数据分析软件选用SPSS 22.0,计数资料以%表示,采用 χ^2 检验。计量资料以($\bar{x} \pm s$)表示,采用t检验。以Pearson相关性分析尿液NGAL水平与RRI、APACHE II评分的关系。通过多因素Logistic回归分析脓毒症合并AKI患者28 d死亡的影响因素。 $P < 0.05$ 表示差异有统计学意义。

2 结果

2.1 两组尿液NGAL水平、RRI、APACHE II评分对比

AKI组尿液NGAL水平、RRI、APACHE II评分均明显高于非AKI组(均 $P < 0.05$),见表1。

2.2 尿液NGAL水平与RRI、APACHE II评分的相关性分析

经Pearson相关性分析可得,尿液NGAL水平与RRI、APACHE II评分均呈正相关(均 $P < 0.05$),见表2。

2.3 死亡组与存活组尿液NGAL水平、基线资料、SOFA评分以及实验室指标对比

将AKI组患者按照随访28 d时是否死亡分为死亡组32例和存活组84例。死亡组AKI分期2~3期人数占比高于存活组,且SOFA评分、APACHE II评分以及尿液NGAL、尿Kim-1水平均高于存活组,而尿CysC水平低于存活组(均 $P < 0.05$),见表3。

表 1 两组尿液 NGAL 水平、RRI、APACHE II 评分对比($\bar{x} \pm s$)Table 1 Comparison of urine NGAL level, RRI and APACHE II score between the two groups($\bar{x} \pm s$)

Groups	n	Urine NGAL(ng/mL)	RRI	APACHE II score(scores)
AKI group	116	91.27 $\pm$ 30.59	0.73 $\pm$ 0.08	27.61 $\pm$ 3.22
Non AKI group	135	60.48 $\pm$ 14.67	0.55 $\pm$ 0.04	24.58 $\pm$ 2.83
t	-	10.389	23.013	7.934
P	-	0.000	0.000	0.000

表 2 尿液 NGAL 水平与 RRI、APACHE II 评分的相关性分析

Table 2 Correlation analysis of urine NGAL level and RRI, APACHE II score

Related indicators	Urine NGAL level	
	r	P
RRI	0.613	0.000
APACHE II score	0.629	0.000

表 3 死亡组与存活组尿液 NGAL 水平、基线资料、SOFA 评分以及实验室指标对比

Table 3 Comparison of urine NGAL level, baseline data, SOFA score and laboratory indicators between death group and survival group

Items		Death group (n=32)	Survival group (n=84)	χ^2/t	P
Gender	Male	19(59.38)	46(54.76)	0.200	0.655
	Female	13(40.62)	38(45.24)		
Age (years)	<50	15(46.88)	50(59.52)	1.505	0.220
	≥ 50	17(53.12)	34(40.48)		
AKI staging	Stage 1	10(31.25)	55(65.48)	11.018	0.001
	Stage 2~3	22(68.75)	29(34.52)		
SOFA score (scores)		12.05 $\pm$ 2.34	9.02 $\pm$ 1.97	7.022	0.000
Urine NGAL(ng/mL)		112.34 $\pm$ 35.47	83.87 $\pm$ 26.34	4.708	0.000
RRI		0.82 $\pm$ 0.10	0.69 $\pm$ 0.07	7.892	0.000
APACHE II score (scores)		30.62 $\pm$ 4.22	26.58 $\pm$ 3.10	5.652	0.000
Urinary Kim-1(μ g/L)		84.22 $\pm$ 15.29	40.83 $\pm$ 10.83	17.113	0.000
Urinary CysC(mg/L)		2.10 $\pm$ 0.42	6.73 $\pm$ 1.32	19.424	0.000

2.4 脓毒症合并 AKI 患者 28d 死亡影响因素的多因素 Logistic 回归分析

以脓毒症合并 AKI 患者 28d 时死亡与否为因变量,赋值如下:死亡=1,存活=0。以 AKI 分期、SOFA 评分、尿液 NGAL、RRI、APACHE II 评分、尿 Kim-1、尿 CysC 为自变量,赋值如下:AKI 分期 1 期=0,2~3 期=1;SOFA 评分、APACHE II 评分以及尿液 NGAL、尿 Kim-1、尿 CysC 均为原值输入。经多因素 Logistic 回归分析发现:AKI 分期 2~3 期、SOFA 评分、APACHE II 评分以及尿液 NGAL、尿 Kim-1 均是脓毒症合并 AKI 患者 28d 死亡的危险因素,而尿 CysC 为其保护因素(均 $P<0.05$),见表 4。

3 讨论

脓毒症是人体对感染反应失调导致的器官功能障碍综合征,主要表现为寒战、发热(或低体温)、心慌、气促及精神状态改变等症状,可导致器官功能不全及循环障碍,往往累及肾脏,

是 AKI 发生的独立危险因素^[14,15]。AKI 在脓毒症患者中的发病率以及病死率均较高,所以,对 AKI 的准确诊断以及预后评估是提高患者救治成功率的重中之重^[16-18]。尽管近年来针对脓毒症合并 AKI 的研究和治疗取得极大的进展,但该类患者的病死率仍居高不下,其主要原因之一是缺乏对脓毒症患者早期诊断 AKI 敏感性、特异性较高的生物标志物,从而导致最佳治疗时间的延误,最终促使病情进展并形成不可逆损伤^[19-21]。既往,临床上主要依赖血肌酐、尿素氮等指标进行患者肾功能变化情况的评估,但上述指标无法避免非肾因素的影响,而 SOFA 以及 APACHE II 评分应用于 AKI 的评估中具有一定的滞后性^[22-24]。因此,寻找能够早期准确诊断脓毒症合并 AKI 的指标显得尤为重要。

本研究发现,AKI 组尿液 NGAL 水平、RRI、APACHE II 评分均明显高于非 AKI 组。分析原因可能在于 NGAL 最早是在活化的中性粒细胞中被发现,同时可在近端肾小管细胞等多种上皮细胞中分泌,正常生理状态下,NGAL 在肾组织中极少表

表 4 脓毒症合并 AKI 患者 28 d 死亡影响因素的多因素 Logistic 回归分析

Table 4 Multivariate Logistic regression analysis of influencing factors of 28 d death in patients with sepsis complicated with AKI

Risk factors	Regression coefficient	Standard error	P	OR	95%CI
AKI Stage 2~3	4.051	2.745	0.013	1.441	1.032~2.075
SOFA score	3.184	3.273	0.000	1.304	1.105~3.311
Urine NGAL	2.277	2.630	0.008	2.276	1.973~2.236
RRI	1.989	3.106	0.021	1.157	1.047~1.537
APACHE II score	2.733	2.475	0.001	2.345	2.015~3.344
Urinary Kim-1	3.284	3.185	0.000	2.873	2.455~3.945
Urinary CysC	0.155	0.123	0.003	0.822	0.712~0.955
Constant term	-5.253	2.301	0.002	0.001	-

达,但可在 AKI 发生的超早期肾脏远端肾上皮细胞中表达,是尿液中 NGAL 的重要来源,因此可直接反映肾损伤的严重程度^[25,26]。超声检测 RRI 是诊断 AKI 的有效手段,具有操作简单、无创等特点,且能较为清晰地观察肾组织血管数量、血流分布、大小、流速以及方向等,可为临床 AKI 的诊治提供参考依据^[27,28]。APACHE II 评分则是目前用以评估危重症患者病情严重程度的评分系统之一,可较为准确、客观地预测危重症患者的预后^[29,30]。进一步研究发现,尿液 NGAL 水平与 RRI、APACHE II 评分均呈正相关,这提示了在临床实际工作中可通过联合检测上述各项指标早期预测 AKI。本研究还发现 AKI 分期 2~3 期、SOFA 评分、APACHE II 评分以及尿液 NGAL、尿 Kim-1 均是脓毒症合并 AKI 患者 28d 死亡的危险因素,而尿 CysC 为其保护因素。究其原因可能是随着 AKI 分期以及 SOFA 评分、APACHE II 评分的升高,患者的病情往往较为严重,临床治疗难度较高,预后较差。NGAL 属于新型脂蛋白之一,可通过和中性粒细胞明胶酶共价结合,在正常生理状态表达量极少,但肾脏出现缺血性损伤时,其分泌量迅速升高,从而导致尿液中 NGAL 浓度上升。Kim-1 作为新型跨膜糖蛋白之一,往往表达于 AKI 的近端肾小管上皮细胞,且其水平并不受慢性肾病、尿路感染等因素的影响,随着其表达水平的不断升高,反映了患者的病情的加剧,导致患者预后不良。CysC 广泛分布在人体多种体液内,且在近曲小管内会被分解,从而在肾小球中自由滤过,最终排出体外,但 AKI 发生时,尿 CysC 浓度降低,且水平降低越明显,预示患者病情越严重,预后不良。

综上所述,尿液 NGAL 在脓毒症合并 AKI 患者中存在明显高表达,且和 RRI、APACHE II 评分及 28d 病死率密切相关,值得临床关注。

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(上接第 2981 页)

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