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血清 TRAF-6、MCP-1、sTREM-1、IL-33 水平与脓毒症严重程度及与合并急性肾损伤关系的临床分析 *

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摘要 目的：探讨脓毒症患者血清肿瘤坏死因子受体相关因子(Tumor necrosis factor receptor-related factor，TRAF)-6、单核细胞趋化蛋白(Monocyte chemotactic protein，MCP)-1、可溶性髓样细胞触发受体(Soluble myeloid cell trigger receptor，sTREM)-1、白介素(Interleukin，IL)-33 水平的变化及与病情严重程度及合并急性肾损伤(acute kidney injury, AKI)的相关性。**方法：**选择 2014 年 2 月到 2018 年 7 月在我医院 ICU 病房进行诊治的脓毒症患者 145 例，分析脓毒症相关性急性肾损伤(sepsis-associated AKI，SAKI)的发生情况，比较 SAKI 和非 SAKI 患者血清 TRAF-6、MCP-1、sTREM-1、IL-33 水平，采用 Pearson 相关分析血清 TRAF-6、MCP-1、sTREM-1、IL-33 含量与 APACHE Ⅱ评分、SOFA 评分的相关性，多因素 logistic 回归分析脓毒症患者发生 SAKI 的影响因素。**结果：**在 145 例患者中，发生 SAKI 者 69 例，发生率为 47.6%。SAKI 组患者的年龄、性别、原发病、白细胞(white blood cell，WBC)计数、C 反应蛋白(C reactive protein，CRP)、降钙素原(procalcitonin，PCT)、体重指数、BUN、Scr 与 eGFR 值与非 SAKI 组患者对比差异均无统计学意义(P<0.05)。SAKI 组患者 APACHE Ⅱ评分、SOFA 评分血清 TRAF-6、MCP-1、sTREM-1、IL-33 含水平含量均显著高于非 SAKI 组患者(P<0.05)。Pearson 相关性分析显示血清 TRAF-6、MCP-1、sTREM-1、IL-33 水平与 SAKI 患者的急性生理和慢性健康Ⅱ(acute physiology and chronic health evaluation II，APACHE Ⅱ)评分、序贯多器官功能障碍(sequential organ failure assessment，SOFA) 评分均呈显著正相关性 (P<0.05)。logistic 回归分析显示血清 TRAF-6、MCP-1、sTREM-1、IL-33 水平升高均为影响 SAKI 发生的独立危险因素(P<0.05)。**结论：**血清 TRAF-6、MCP-1、sTREM-1、IL-33 水平与脓毒症严重程度显著相关，可能作为诊断和治疗 SAKI 的参考指标及干预靶点。

关键词：脓毒症；急性肾损伤；TRAF-6；MCP-1；sTREM-1

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Clinical Analysis of the Relationship between Serum TRAF-6, MCP-1, sTREM-1, IL-33 and Severity of Sepsis and Acute Kidney Injury*

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ABSTRACT Objective: To investigate the changes of tumor necrosis factor receptor-related factor (TRAF)-6, monocyte chemotactic protein (MCP)-1, soluble myeloid cell triggering receptor (sTREM)-1, interleukin (IL)-33 levels in patients with sepsis and their correlation with the severity of disease and acute kidney injury (AKI). **Methods:** A total of 145 patients with sepsis who were treated in the ICU ward of our hospital from February 2014 to July 2018 were enrolled. The incidence of sepsis-associated acute kidney injury (SAKI) were analyzed. SAKI were compared. Serum levels of TRAF-6, MCP-1, sTREM-1, and IL-33 in patients with non-SAKI, and Pearson correlation analysis of serum TRAF-6, MCP-1, sTREM-1, IL-33 and APACHE II scores, SOFA scores Correlation, multivariate logistic regression analysis of the influencing factors of SAKI in patients with sepsis. **Results:** Of the 145 patients, 69 had SAKI, an incidence of 47.6%. Age, gender, primary disease, white blood cell (WBC) count, C reactive protein (CRP), procalcitonin (PCT), body mass index, BUN, Scr and There were no significant difference between the eGFR value and the non-SAKI group (P<0.05). The APACHE II score, SOFA score, serum TRAF-6, MCP-1, sTREM-1, and IL-33 levels in the SAKI group were significantly higher than those in the non-SAKI group(P<0.05). Pearson correlation analysis showed serum TRAF-6, MCP-1, sTREM-1, IL-33 levels and acute physiology and chronic health evaluation II (APACHE II) scores in SKI patients, sequential multiple organs Sequential organ failure assessment (SOFA) scores were significantly positively correlated (P<0.05). Logistic regression analysis showed that elevated levels of serum TRAF-6, MCP-1, sTREM-1, and IL-33 were independent risk factors for SAKI (P<0.05). **Conclusion:** The serum TRAF-6, MCP-1, sTREM-1, and IL-33 levels were significantly associated with the severity of sepsis and may serve as references for the diagnosis and treatment of SAKI.

Key words: Sepsis; Acute kidney injury; TRAF-6; MCP-1; sTREM-1

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前言

脓毒症(sepsis)是由休克、创伤、大手术等原因导致的严重并发症,多需要在重症监护病房(intensive care unit,ICU)诊治,是临床上危重患者死亡的重要原因之一[1,2]。肾功能损伤是脓毒症最常导致的器官功能障碍,约 50%的急性肾损伤(acute kidney injury,AKI)是由脓毒症所致[3]。脓毒症相关的急性肾损伤(sepsis association AKI,SAKI)预后更差,住院时间和住 ICU 时间更长[4]。SAKI 的病情判断与早期预测对提高改善预后具有重要价值,特别是 SAKI 具有可逆性,临床医师正确采取有效的干预措施,可有逆转肾功能损害,减轻病死率[5,6]。但 TAKI 的发病机制非常复杂,涉及肾小管损伤、内皮细胞微脉管、氧化应激、免疫应答系统导致的肾小管细胞损伤的复杂病理生理过程[7]。

SAKI 的早期诊断依赖于敏感度和特异性高的生物标志物检测,肿瘤坏死因子受体相关因子(Tumor necrosis factor receptor-related factor,TRAF)-6 是 Toll 样受体介导的先天免疫反应介导的信号通路中一个关键的衔接蛋白,可诱导炎症细胞因子和黏附因子等基因的表达 [8,9]。单核细胞趋化蛋白(Monocyte chemotactic protein,MCP)-1 为机体的遗传易感基因,在脓毒症的发生与临床转归中发挥重要的作用[10]。可溶性髓样细胞触发受体 (Soluble myeloid cell trigger receptor,sTREM)-1 是与炎症相关的免疫球蛋白超家族中的一种,sTREM-1 由激活的吞噬细胞释放后进入人体体液中,sTREM-1 浓度可以用于判断相关疾病的感染严重程度[11]。脓毒症患者普遍存在慢性微炎性反应状态,易出现心血管并发症、感染、贫血与营养不良[12,13]。在微炎性反应状态下,脓毒症患者白介素(Interleukin,IL)-33 分泌量增加,会出现免疫抑制,进一步加重炎症反应[14]。因此,本研究主要探讨了脓毒症患者血清 TRAF-6、MCP-1、sTREM-1、IL-33 水平的变化及与病情严重程度及合并急性肾损伤的相关性,结果报道如下。

1 对象与方法

1.1 研究对象

选择 2014 年 2 月到 2018 年 7 月在我医院 ICU 病房进行诊治的脓毒症患者 145 例。纳入标准:符合脓毒症的诊断标准;经过授权委托人知情同意签字;被医院伦理委员批准进行此次研究;首次入住 ICU,发病到入院时间≤ 48 h。排除标准:不配合治疗,资料不全者;入院后 24h 内死亡者;妊娠或哺乳期妇女;妊娠产妇;恶性肿瘤、血液系统疾病患者;病毒性肝炎、艾滋病等传染性疾病患者;1 个月内使用大剂量激素的患者。

1.2 血清 TRAF-6、MCP-1、sTREM-1、IL-33 水平的检测

采集所有患者入院后静脉血样本，静置 30 min,4℃下 3000 rpm 离心 15min (离心半径 13 cm)，上清的血清标本用 -80℃储存，采用酶联免疫吸附法检测血清 TRAF-6、MCP-1、sTREM-1、IL-33 含量。检测试剂盒都购自上海生工公司,且上述指标均由专业人员在说明书指导下严格操作。

1.3 数据收集

记录所有患者入院 ICU 的基本资料,包括年龄、性别、原发病、肾功能指标(BUN、Scr、eGFR)等,同时记录白细胞计数(white blood cell,WBC) 计数、C 反应蛋白 (C reactive protein,CRP)、降钙素原(procalcitonin,PCT)、急性生理和慢性健康Ⅱ(acute physiology and chronic health evaluation II,APACHE Ⅱ)评分、序贯多器官功能障碍(sequential organ failure assessment,SOFA)评分、体重指数等指标。

1.4 ASKI 的诊断标准

SAKI:48h 内肾功能急剧下降，表现为 SCr 上升 >50%或尿量减少≧6 h。

1.5 统计学分析

选择 SPSS19.00 软件进行数据分析,计量资料以均数± 标准差表示,组间比较采用 t 检验,计数资料以率表示,组间比较采用 x^2 检验，两变量间的相关性采用 Spearman 相关分析,影响因素分析采用 logistic 回归分析,以 P<0.05 为差异具有统计学意义。

2 结果

2.1 SAKI 的发生情况

在 145 例患者中,发生 SAKI 69 例,发生率为 47.6%。

2.2 SAKI 和非 SAKI 患者一般临床资料对比

SAKI 组患者的年龄、性别、原发病、WBC 计数、CRP、PCT、体重指数等与非 SAKI 组患者的一般资料对比差异无统计学意义(P<0.05),具有可比性。

2.3 SAKI 和非 SAKI 患者肾功能与病情的比较

SAKI 组患者的 BUN、Scr 与 eGFR 值与非 SAKI 组患者对比差异无统计学意义(P>0.05),但 APACHE Ⅱ评分与 SOFA 评分都显著高于非 SAKI 组患者(P<0.05)。见表 1。

表 1 SAKI 和非 SAKI 患者肾功能与病情评分的对比(均数± 标准差)

Table 1 Comparison of the renal function and disease scores between the SAKI group and non SAKI group (mean ± standard deviation)

Groups	n	BUN(mmol/L)	Scr(μmol/L)	eGFR (mL/min.1.73 m²)	APACHE Ⅱ scores (points)	SOFA scores (points)
SAKI group	69	6.31± 1.33	77.20± 10.44	86.23± 10.41	18.53± 2.14	9.51± 0.44
Non-SAKI group	76	6.18± 0.49	73.65± 11.62	83.00± 8.49	15.00± 1.47	7.87± 0.81
t		0.382	2.104	1.889	7.204	5.672
P		0.511	0.089	0.122	0.013	0.024

2.4 SAKI 和非 SAKI 患者血清 TRAF-6、MCP-1、sTREM-1、IL-33 含量对比

AKI 组患者的血清 TRAF-6、MCP-1、sTREM-1、IL-33 含量含量都显著高于非 SAKI 组患者(P<0.05),见表 2。

表 2 两组血清 TRAF-6、MCP-1、sTREM-1、IL-33 含量的对比(均数± 标准差)

Table 2 Comparison of the serum TRAF-6, MCP-1, sTREM-1, and IL-33 levels between the SAKI group and non SAKI group (mean± standard deviation)

Groups	n	TRAF-6(ng/mL)	MCP-1(ng/mL)	sTREM-1(pg/mL)	IL-33(ng/mL)
SAKI group	69	137.22± 11.48	546.20± 156.29	561.49± 200.72	45.02± 10.85
Non-SAKI group	76	78.55± 10.89	345.76± 105.29	341.09± 78.10	22.18± 8.25
t		15.922	23.582	34.882	15.022
P		0.000	0.000	0.000	0.000

2.5 血清 TRAF-6、MCP-1、sTREM-1、IL-33 含量与 APACHE Ⅱ评分、SOFA 评分的相关性

145 例患者血清 TRAF-6、MCP-1、sTREM-1、IL-33 含量与 APACHE Ⅱ评分、SOFA 评分均呈显著正相关性(P<0.05),见表3。

表 3 脓毒症患者血清 TRAF-6、MCP-1、sTREM-1、IL-33 含量与 APACHE Ⅱ评分和 SOFA 评分的相关性(n=145)

Table 3 Correlation between the serum TRAF-6, MCP-1, sTREM-1, and IL-33 levels and the APACHE Ⅱ, SOFA scores in the patients with sepsis (n=145)

Groups	TRAF-6	MCP-1	sTREM-1	IL-33
APACHE Ⅱ scores-r	0.544	0.482	0.421	0.389
P	0.002	0.011	0.021	0.027
SOFA scores-r	0.672	0.522	0.488	0.411
P	0.000	0.004	0.006	0.022

2.6 SAKI 的影响因素分析

在 145 例患者中,以发生 SAKI 作为因变量,以调查数据资料、血清学检测等作为自变量,logistic 回归分析显示血清 TRAF-6、MCP-1、sTREM-1、IL-33 水平都为影响 SAKI 发生的独立危险因素(P<0.05),见表 4。

表 4 影响脓毒症患者发生 SAKI 的多因素分析(n=145)

Table 4 Multivariate analysis of SAKI in patients with sepsis (n=145)

Index	Area under the curve	Standard error	*P*	95%CI	
				Lower	Upper
TRAF-6	0.671	0.064	0.025	0.489	0.823
MCP-1	0.562	0.193	0.000	1.942	3.933
sTREM-1	0.513	0.089	0.009	0.633	0.913
IL-33	0.781	0.433	0.000	2.984	9.111

3 讨论

脓毒症是失控炎症反应导致的可危及生命的临床综合征,也是 ICU 重症患者死亡的主要原因之一[15]。肾功能损伤是脓毒症最常导致的器官功能障碍,已成为肾功能损伤的重要原因之一[16]。本研究显示 SAKI 组患者的 APACHE Ⅱ评分与 SOFA 评分都显著高于非 SAKI 组患者,表明 SAKI 可使脓毒症患者的预后变差。相关研究也显示脓毒症患者急性肾损伤患者的病死率与急性肾损伤严重程度呈正相关性[17]。

早期诊断 SAKI 对改善脓毒症的预后的具有重要意义。研究表明蛋白在肾脏血流量不足时易沉积于管腔,使小球基底膜通透性下降,有效滤过面积减少,容量不足,导致肾功能受损[18]。有研究显示年龄、氧化应激增强、患者氧自由基、机械通气等是患者肾脏损害的高危险因素,炎症介质通过引起肾血流动力学异常也可造成肾脏的损害[19]。目前认为理想化的生物标志物应具备以下特征:(1)不需要连续监测;(2)有标准化检测方式,具有较高的灵敏性和特异性;(3)具有预测价值;(4)不依赖于 GFR 的下降和基础疾病等;(5)检测方法便捷[20]。目前,诊断肾功能损伤的指标主要为 BUN、Scr 与 eGF 等,不过 SCr 等指标不能确切地反映 GFR,因为 GFR 受小管 SCr 分泌和非肾性因素影响,SCr 的分泌也受年龄、性别、体重、活动状态、饮食、药物、肝功能等多重因素影响[21,22]。本研究显示 SAKI 组患者的 BUN、Scr 与 eGFR 值与非 SAKI 组患者对比差异无统计学意义,说明常规指标对鉴别诊断 SAKI 与脓毒症的效果比较差。

SAKI 的发生机制目前仍未完全阐明。TRAF-6 在病原体诱导的炎症应答过程中起核心作用,其的遗传变异很可能会影响脓毒症的发生风险和病程进展。正常人肾脏组织 TRAF-6 均呈低表达状态,但在肾小管上皮细胞受到损伤时,其表达显著增高[23]。TRAF-6 能够调节再生细胞间的粘附及细胞内吞作用,产生的可溶性片段从细胞上脱落进入尿液中,因而被是肾脏损伤的早期标志物[24]。MCP-1 是单核细胞、肾小管上皮细胞分泌的强效化学激活合成物,能刺激炎症因子与 NF-κB 的活性,从而

控制 SAKI 的表达[25]。sTREM-1 的相对分子量为 26KD,编码 8 种受体,它由胞外域、跨膜域、胞浆域等共同组成,主要表达于中性粒细胞、巨噬细胞、单核细胞的表面[26]。TREM-1 可以协同微生物产物调节急性炎症反应,由激活的吞噬细胞释放后进入人体体液中,可以用于判断相关疾病的感染严重程度[27]。本研究显示脓毒症 SAKI 组患者在入室时血清 sTREM-1 的表达水平非高于非 SAKI 组患者,而此时临床评价肾功能的指标 Scr、eGFR 则无显著变化,推测 SAKI 组患者此时已有肾小管上皮细胞的轻微受损,但尚未引起 Scr、BUN、eGFR 值的变化[28]。还有学者描述脓毒症患者血浆 sTREM-1 的时间变化趋势,发现血清 sTREM-1 水平的迅速下降也可以反映脓毒症患者有好的预后,对脓毒症休克患者的预后有一定的预测价值[29,30]。IL-33 是急性反应期炎症介质,通过诱导 hs-CRP 的合成免疫复合物沉积在血管壁并激活补体,诱发对血管的免疫炎性损伤[31]。此外,IL-33 是炎症反应的最初启动者,能诱发前列腺素、白三烯、血小板激活因子、IL-1、IL-6 及 IL-8 等次级炎症介质合成[32]。本研究结果显示 AKI 组患者的血清 TRAF-6、MCP-1、sTREM-1、IL-33 含量含量都显著高于非 SAKI 组患者,提示其水平升高可能促进了脓毒症患者 AKI 的发生。

APACHE Ⅱ评分、SOFA 评分是反映患者病情的金标准,但是都存在一定的缺陷,需要手工计算和数据繁杂而影响利用[33]。有学者比较分析示 SAKI 患者和非 SAKI 组调节因子表达与前炎症细胞因子表达水平的关系,正性调节因子越高,负性调节因子越低,SAKI 组正性调节因子显著高于非 SAKI 组,负性调节因子低于非 SAKI 组。而多靶点调控炎症因子表达而阻断前炎症细胞因子的级联反应有助于脓毒症患者的恢复[34-36]。本研究显示脓毒症患者血清 TRAF-6、MCP-1、sTREM-1、IL-33 含量与其 APACHE Ⅱ评分、SOFA 评分都呈正相关性,且血清 TRAF-6、MCP-1、sTREM-1、IL-33 水平都为影响 SAKI 发生的主要独立危险因素,提示其可能作为预测 SAKI 的参考指标和治疗靶点。

综上所述,脓毒症患者多伴随有 SAKI,可导致血清 TRAF-6、MCP-1、sTREM-1、IL-33 表达上升,其与脓毒症严重程度显著相关,可能作为诊断和治疗 SAKI 的参考指标及干预靶点。当然,本研究也存在一定不足,没有对患者血清 TRAF-6、MCP-1、sTREM-1、IL-33 进行动态检测,未设置健康对照组,且影响患者预后的影响比较多,将在下一步进行多中心、多样本、多指标分析。

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