

doi: 10.13241/j.cnki.pmb.2020.10.041

脓毒症患者血清 HMGB1、IGF-1 水平变化及与 T 淋巴细胞亚群、预后的关系研究 *

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摘要 目的:探讨脓毒症患者血清高迁移率族蛋白 1(HMGB1)、胰岛素样生长因子-1(IGF-1)水平变化及与 T 淋巴细胞亚群、预后的关系。**方法:**选取 2016 年 2 月~2018 年 12 月期间我院收治的脓毒症患者 139 例,根据 Sepsis 3.0 定义,将脓毒症患者分成一般脓毒症组($n=73$)及脓毒症休克组($n=66$),根据患者进入重症监护室 28d 后的转归资料,将其分为存活组和死亡组。比较不同预后、不同病情严重程度的脓毒症患者血清 IGF-1、HMGB1 水平、急性病生理与慢性健康评价系统 II (APACHE II)评分以及 T 淋巴细胞亚群;采用 Pearson 相关分析血清 HMGB1、IGF-1 水平与 T 淋巴细胞亚群、APACHE II 评分的关系。**结果:**一般脓毒症组 $CD3^+$ 、 $CD4^+$ 、 $CD4^+/CD8^+$ 高于脓毒症休克组, $CD8^+$ 低于脓毒症休克组($P<0.05$)。脓毒症休克组血清 HMGB1 水平、APACHE II 评分均高于一般脓毒症组,血清 IGF-1 水平则低于一般脓毒症组($P<0.05$)。存活组 $CD8^+$ 低于死亡组, $CD3^+$ 、 $CD4^+$ 、 $CD4^+/CD8^+$ 高于死亡组($P<0.05$)。存活组血清 HMGB1 水平、APACHE II 评分低于死亡组,血清 IGF-1 水平高于死亡组($P<0.05$)。Pearson 相关分析显示,脓毒症患者血清 HMGB1 水平与 $CD8^+$ 、APACHE II 评分呈正相关,与 $CD3^+$ 、 $CD4^+$ 、 $CD4^+/CD8^+$ 呈负相关($P<0.05$);血清 IGF-1 水平与 $CD8^+$ 、APACHE II 评分呈负相关,与 $CD3^+$ 、 $CD4^+$ 、 $CD4^+/CD8^+$ 呈正相关($P<0.05$)。**结论:**脓毒症血清 HMGB1、T 淋巴细胞亚群、IGF-1 均存在异常变化,可用于评估脓毒症患者的病情和预后。

关键词:高迁移率族蛋白 1;脓毒症;胰岛素样生长因子-1;T 淋巴细胞亚群;预后;关系

中图分类号:R631.2 文献标识码:A 文章编号:1673-6273(2020)10-1984-04

Changes of Serum HMGB1 and IGF-1 Levels in Sepsis Patients and Their Relationship with T Lymphocyte Subsets and Prognosis*

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ABSTRACT Objective: To investigate the changes of serum high mobility group protein 1 (HMGB1) and insulin-like growth factor-1 (IGF-1) levels in sepsis patients and their relationship with T lymphocyte subsets and prognosis. **Methods:** 139 sepsis patients who were admitted to our hospital from February 2016 to December 2018 were selected. According to defined by sepsis 3.0, sepsis patients were divided into general sepsis group ($n=73$) and sepsis shock group ($n=66$). According to the outcome data after 28 days in ICU, the patients were divided into survival group and death group. The serum IGF-1, HMGB1 levels, acute disease physiology and chronic health assessment system II (APACHE II) scores and T lymphocyte subsets were compared in sepsis patients with different severity and prognosis. Pearson correlation analysis was used to analyze the relationship between serum HMGB1, IGF-1 levels and T lymphocyte subsets, APACHE II scores. **Results:** The $CD8^+$, $CD4^+$, $CD4^+/CD8^+$ in general sepsis group were higher than those in septic shock group, and $CD8^+$ was lower than that in septic shock group ($P<0.05$). The serum HMGB1 level and APACHE II scores in septic shock group were higher than those in general septic group, while the serum IGF-1 level was lower than that in general septic group ($P<0.05$). $CD8^+$ in the survival group was lower than that in the death group, and $CD3^+$, $CD4^+$, $CD4^+/CD8^+$ were higher than those in the death group($P<0.05$). The serum HMGB1 level and APACHE II scores in the survival group were lower than those in the death group, and the serum IGF-1 level was higher than that in the death group ($P<0.05$). Pearson correlation analysis showed that HMGB1 was positively correlated with $CD8^+$, APACHE II scores, negatively correlated with $CD3^+$, $CD4^+$, $CD4^+/CD8^+$ ($P<0.05$). Serum IGF-1 level was negatively correlated with $CD8^+$, APACHE II scores, and positively correlated with $CD3^+$, $CD4^+$, $CD4^+/CD8^+$ ($P<0.05$). **Conclusion:** There are abnormal changes in serum HMGB1, T lymphocyte subsets and IGF-1 in sepsis patients. It can be used to evaluate the condition and prognosis of sepsis patients.

Key words: High mobility group protein 1; Sepsis; Insulin-like growth factor-1; T lymphocyte subsets; Prognosis; Relationship

Chinese Library Classification(CLC): R631.2 **Document code:** A

Article ID: 1673-6273(2020)10-1984-04

* 基金项目:河北省医学科学研究项目(20162720)

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(收稿日期:2020-02-06 接受日期:2020-02-28)

前言

脓毒症是由感染所引起的机体持续性、失控性炎症反应,严重时可导致器官功能障碍和(或)循环障碍^[1]。既往有研究结果显示^[2],约有40%的脓毒症病人最后可发展至脓毒症性急性肾损伤,且其病死率高达70%,患者预后极差。以往传统观点认为^[3],早期炎症介质瀑布式释放是导致脓毒症患者死亡的主要原因,随着研究的深入,越来越多的早期拮抗炎症细胞因子的措施被应用于临床,但因其狭窄的治疗时间窗而收效甚微。因此,人们开始寻找具备更有效、更宽松的治疗时间窗的新因子。高迁移率族蛋白1(High mobility group box 1, HMGB1)属于高迁移率族蛋白家族一员,具有促炎效应^[4]。胰岛素样生长因子-1 (Insulin-like growth factor-1, IGF-1) 是一种作用于多种组织和器官的多效性细胞营养因子,以往相关研究表明^[5],急性应激反应可导致机体 IGF-1 水平发生变化。但现临床鲜有关于 HMGB1、IGF-1 与脓毒症患者免疫功能和预后关联性的报道。鉴于此,本文通过探讨脓毒症患者血清 HMGB1、IGF-1 水平变化及与 T 淋巴细胞亚群、预后的关系,以期对临床脓毒症的病情判断和预后评估提供参考。

1 资料和方法

1.1 一般资料

选取我院于2016年2月~2018年12月期间收治的139例脓毒症患者,纳入标准:(1)均符合 Sepsis 3.0 定义^[6]中有关脓毒症的相关诊断标准;(2)临床资料完整者;(3)患者家属知情本次研究且已签署了同意书。排除标准:(1)合并恶性肿瘤、精神疾病和传染性疾病者;(2)急性胰腺炎,但明确无感染者;(3)慢性疾病终末期患者;(4)伴有自身免疫性疾病或免疫功能异常者。分级诊断标准^[7]:脓毒性休克:经充分液体复苏但仍未能纠正低组织灌注和低血压等情况。一般脓毒症:满足下列中的两条:心率>90次/min,体温>38℃或<36℃,白细胞计数>12×10⁹/L或<4×10⁹/L,呼吸>20次/min或PCO₂<32 mmHg。根据分级诊断标准将脓毒症患者分成一般脓毒症组(n=73)及脓毒症休克组(n=66),其中一般脓毒症组男43例,女30例,年龄32~59岁,平均(46.28±5.38)岁。脓毒症休克组男40例,女

26例,年龄30~60岁,平均(47.06±5.49)岁。两组患者性别比例、年龄分布比较差异无统计学意义($P>0.05$)。收集139例患者进入重症监护室28d后的转归资料,其中死亡者38例,记为死亡组,存活者101例,记为存活组。本次研究已获取我院伦理学委员会批准同意。

1.2 方法

(1)标本采集及检测:所有患者分别于入院次日采集清晨空腹肘静脉血6 mL,血标本常温下3200 r/min离心15 min,有效离心半径10 cm,分离出血清,存于-30℃冰箱待测。采用流式细胞仪(上海旭东海普药业有限公司生产)检测T淋巴细胞亚群:CD3⁺、CD4⁺、CD8⁺,并计算CD4⁺/CD8⁺。采用全自动微粒子化学发光免疫分析系统(美国 Beckman 公司)检测 IGF-1。采用酶联免疫吸附法检测 HMGB1,严格遵守试剂盒(浙江蓝森生物科技有限公司)说明书进行操作。(2)APACHE II 评分^[8]:所有患者于入院24 h内完成急性病生理与慢性健康评价系统 II (Acute Physiology and Chronic Health Evaluation II, APACHE II) 评分,分值越高表示病情越严重,理论分值上限为71分。

1.3 观察指标

比较不同病情严重程度的脓毒症患者的血清 HMGB1、IGF-1 水平、T 淋巴细胞亚群、APACHE II 评分;比较不同预后脓毒症患者的血清 HMGB1、IGF-1 水平、T 淋巴细胞亚群、APACHE II 评分。

1.4 统计学方法

采用 SPSS25.0 统计学软件进行统计分析,计量资料采用均数±标准差($\bar{x} \pm s$)描述,采用 t 检验;计数资料采用%表示,实施卡方检验,采用 Pearson 相关分析血清 HMGB1、IGF-1 水平与 T 淋巴细胞亚群、APACHE II 评分的相关性,检验标准设置为 $\alpha=0.05$ 。

2 结果

2.1 不同病情严重程度的脓毒症患者的 T 淋巴细胞亚群变化比较

一般脓毒症组 CD3⁺、CD4⁺、CD4⁺/CD8⁺ 高于脓毒症休克组,CD8⁺ 低于脓毒症休克组($P<0.05$);详见表1。

表1 不同病情严重程度的脓毒症患者的 T 淋巴细胞亚群变化比较($\bar{x} \pm s$)

Table 1 Comparison of T lymphocyte subsets in sepsis patients of different severity($\bar{x} \pm s$)

Groups	CD3 ⁺ (%)	CD4 ⁺ (%)	CD8 ⁺ (%)	CD4 ⁺ /CD8 ⁺
General sepsis group(n=73)	56.41±4.75	42.88±4.02	35.71±3.19	1.20±0.25
Sepsis shock group(n=66)	41.24±4.47	29.23±3.94	44.57±4.21	0.66±0.13
t	16.328	21.487	20.659	19.716
P	0.000	0.000	0.000	0.000

2.2 不同病情严重程度的脓毒症患者的血清 HMGB1、IGF-1 水平、APACHE II 评分比较

脓毒症休克组血清 HMGB1 水平、APACHE II 评分均高于一般脓毒症组,血清 IGF-1 水平则低于一般脓毒症组($P<0.05$);详见表2。

2.3 不同预后脓毒症患者的 T 淋巴细胞亚群比较

存活组 CD8⁺ 低于死亡组,CD3⁺、CD4⁺、CD4⁺/CD8⁺ 高于死亡组($P<0.05$);详见表3。

2.4 不同预后脓毒症患者的血清 HMGB1、IGF-1 水平、APACHE II 评分比较

存活组血清 HMGB1 水平、APACHE II 评分低于死亡组,血清 IGF-1 水平高于死亡组($P<0.05$);详见表4。

表 2 不同病情严重程度的脓毒症患者的血清 HMGB1、IGF-1 水平、APACHE II 评分比较($\bar{x} \pm s$)

Table 2 Comparison of serum HMGB1, IGF-1 and APACHE II scores in sepsis patients with different severity($\bar{x} \pm s$)

Groups	HMGB1(μ g/L)	IGF-1(ng/mL)	APACHE II scores(scores)
General sepsis group(n=73)	42.91 $\pm$ 13.07	104.79 $\pm$ 15.81	4.65 $\pm$ 1.72
Sepsis shock group(n=66)	90.79 $\pm$ 14.21	66.86 $\pm$ 15.51	15.68 $\pm$ 1.28
t	20.693	14.252	21.658
P	0.000	0.000	0.000

表 3 不同预后脓毒症患者的 T 淋巴细胞亚群比较($\bar{x} \pm s$)

Table 3 Comparison of T lymphocyte subsets in sepsis patients with different prognosis($\bar{x} \pm s$)

Groups	CD3 ⁺ (%)	CD4 ⁺ (%)	CD8 ⁺ (%)	CD4 ⁺ /CD8 ⁺
Survival group(n=101)	55.68 $\pm$ 5.92	41.92 $\pm$ 2.83	37.24 $\pm$ 4.19	1.13 $\pm$ 0.17
Death group(n=38)	32.01 $\pm$ 5.01	21.73 $\pm$ 2.53	47.04 $\pm$ 5.14	0.44 $\pm$ 0.08
t	21.864	38.548	11.529	24.000
P	0.000	0.000	0.000	0.000

表 4 不同预后脓毒症患者的血清 HMGB1、IGF-1 水平、APACHE II 评分比较($\bar{x} \pm s$)

Table 4 Comparison of serum HMGB1, IGF-1 and APACHE II scores in sepsis patients with different prognosis($\bar{x} \pm s$)

Groups	HMGB1(μ g/L)	IGF-1(ng/mL)	APACHE II scores(scores)
Survival group(n=101)	63.81 $\pm$ 15.62	99.68 $\pm$ 10.72	9.16 $\pm$ 2.66
Death group(n=38)	70.50 $\pm$ 17.22	52.49 $\pm$ 12.56	11.82 $\pm$ 3.41
t	2.188	22.048	4.850
P	0.030	0.000	0.000

2.5 血清 HMGB1、IGF-1 水平与 T 淋巴细胞亚群、APACHE II 评分的关系分析

Pearson 相关分析显示, 脓毒症患者血清 HMGB1 水平与

CD8⁺、APACHE II 评分呈正相关, 与 CD3⁺、CD4⁺、CD4⁺/CD8⁺ 呈负相关($P<0.05$); 血清 IGF-1 水平与 CD8⁺、APACHE II 评分呈负相关, 与 CD3⁺、CD4⁺、CD4⁺/CD8⁺ 呈正相关($P<0.05$); 详见表 5。

表 5 血清 HMGB1、IGF-1 水平与 T 淋巴细胞亚群、APACHE II 评分的关系分析

Table 5 Analysis of the relationship between serum HMGB1, IGF-1 levels and T-lymphocyte subsets, APACHE II scores

Indexes	HMGB1		IGF-1	
	r	P	r	P
CD3 ⁺	-0.542	0.003	0.509	0.010
CD4 ⁺	-0.436	0.026	0.445	0.022
CD8 ⁺	0.492	0.017	-0.464	0.019
CD4 ⁺ /CD8 ⁺	-0.503	0.011	0.573	0.001
APACHE II scores	0.465	0.020	-0.511	0.009

3 讨论

脓毒症病情进展快, 致死率高, 且其发病率呈逐年升高趋势, 据统计, 我国每年新增 300 万脓毒症患者, 且死亡率高达 30%, 而在美国每年约有 75 万人发生脓毒症, 且病死率达到 20%^[9]。可见, 脓毒症的诊断、治疗及预防已成为全球医学界共同面临的难题。以往的研究中认为脓毒症是一种全身性炎症反应, 在脓毒症的发病早期常表现为全身炎症性反应, 促炎因子如白介素 -6、肿瘤坏死因子 - α 曾被认为是导致患者多器官功能障碍的 " 核心因子 ", 大量早期促炎因子的释放会直接导致

机体组织、器官的损伤^[10-12]。不少临床试验应用拮抗促炎因子的治疗措施后, 并没有取得理想的治疗效果^[13-15]。近年来研究发现, 脓毒症进展过程中多数患者会渡过全身炎症性反应时期, 进入持续时间相对较长的免疫抑制状态, 表现为淋巴细胞凋亡、机体的易感性增加, 增加脓毒症患者病死风险^[16-18]。可见脓毒症不仅仅是炎症反应导致的结果, 还是促炎过程与抗炎过程相互作用致使免疫功能紊乱引发的结果^[19-21]。由于早期炎症因子通常在病因作用后的几分钟至 2 h 内释放, 半衰期较短, 导致检测时间窗较窄, 难以做到有效监测^[22]。因此, 寻求有效的检测因子以获得脓毒症患者的全面诊疗信息具有重要的临床意义。

高迁移率蛋白(HMGB)是从小牛胸腺中提取出的一类含量丰富的非组核蛋白,而 HMGB1 是 HMGB 家族中最为普遍,且大量存在于真核细胞中的一类核蛋白^[23-25]。其具有决定核小体结构和稳定性、促进转录因子及对应序列 DNA 结合的作用。既往有研究资料显示^[26],HMGB1 可作为晚期炎症介质,参与关节炎、脓毒症、脑炎等多种疾病的生理病理过程。冯宣云等学者^[27]通过给小鼠腹腔注射纯化的重组 HMGB1,发现其可导致小鼠出现脓毒症样症状,当给小鼠大量注射时,可导致小鼠死亡,同时采用抗 HMGB1 抗体治疗小鼠时,可减少其死亡率。可见 HMGB1 可能是脓毒症发生、发展过程中较为重要的炎症介质。由于脓症患者机体处于持续损伤状态,而神经-内分泌-免疫系统之间存在着极其复杂的网络关系以及双向信息传递。游婷婷等人^[28]研究证实,生长激素对免疫系统有细胞因子样的免疫调节效果,如促进 T 细胞增殖、增强单核巨噬细胞的吞噬功能以及增强 NK 细胞活性等,而生长激素的许多作用需通过介导 IGF-1 产生。有学者研究发现^[29],脓毒症患儿血清 IGF-1 水平显著降低,且 IGF-1 水平的降低还可增加脓毒症时细菌移位频率,加速患儿病情进展。故猜测 IGF-1 可能诱发脓毒症死亡。

本次研究结果中,与一般脓症患者比较,脓毒症休克患者 HMGB1、CD8⁺、APACHE II 评分升高,IGF-1、CD3⁺、CD4⁺、CD4⁺/CD8⁺ 下降,可见脓症患者血清 HMGB1、IGF-1 水平、T 淋巴细胞亚群均存在异常变化,且可有效反映患者病情严重程度。此外,存活组 HMGB1、APACHE II 评分、CD8⁺ 低于死亡组,IGF-1、CD3⁺、CD4⁺、CD4⁺/CD8⁺ 高于死亡组,提示脓症患者中血清 HMGB1、IGF-1 水平、T 淋巴细胞亚群与患者预后息息相关,早期监测上述指标水平有助于预测脓症患者预后。HMGB1 可通过影响树突状细胞功能间接影响 T 细胞增殖、分泌及分化,同时该影响还与 HMGB1 作用时间及剂量有关。而机体感染和急性应激时 IGF-I 水平下降,可能是由于肝脏合成和分泌 IGF-I 减少所致,也可能与机体负氮平衡相关。以往也有研究表明^[30],IGF-1 可诱导淋巴细胞的选择分化和免疫球蛋白的产生。Pearson 相关分析显示,脓症患者 HMGB1、IGF-1 与 T 淋巴细胞亚群、APACHE II 评分均存在明显相关性,提示临床可通过改善血清 HMGB1、IGF-1 水平以改善患者免疫功能抑制状态,阻止病情进展。但目前通过改善血清 HMGB1、IGF-1 水平来治疗脓毒症的研究尚受到伦理学制约,仅停留于细胞试验和动物实验阶段,尚需更多的研究来证实其有效性和安全性。

综上所述,脓症患者血清 HMGB1、IGF-1 水平、T 淋巴细胞亚群均存在异常变化,通过早期检测其水平可评估脓毒症患者的病情和预后,为进一步研究脓毒症的发病机制和干预方法提供了新的方向。

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