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脓毒症患者短期预后的影响因素及 YAP 联合 STAT3 检测的预测价值研究 *

梁 晗¹ 庄成君² 张 茜¹ 牛 畅¹ 任 峰^{1Δ}

(1 大连医科大学附属第二医院检验科 辽宁 大连 116027; 2 大连医科大学附属第二医院重症医学科 辽宁 大连 116027)

摘要 目的:研究脓毒症患者短期预后的影响因素及 Yes 相关蛋白(YAP)联合信号转导子和转录激活子 3(STAT3) 信使 RNA (mRNA)检测的预测价值。**方法:**选择我院 2019 年 3 月~2021 年 1 月收治的 131 例脓毒症患者,将其按照 28d 预后情况的差异分成死亡组以及生存组。比较两组各项基线资料,外周血单个核细胞 YAP、STAT3 mRNA 表达水平。采用多因素 Logistic 回归分析脓毒症患者短期预后的影响因素。此外,通过受试者工作特征(ROC)曲线分析外周血单个核细胞 YAP、STAT3 mRNA 表达预测脓毒症患者短期预后的效能。**结果:**死亡组患者的外周血单个核细胞 YAP、STAT3 mRNA 相对表达量均高于生存组患者($P<0.05$)。死亡组年龄大于生存组,住院时间短于生存组,APACHE II 评分高于生存组,合并基础疾病、机械通气的患者比例高于生存组,差异均有统计学意义($P<0.05$)。多因素 Logistic 回归分析结果显示,年龄、APACHE II 评分、合并基础疾病、机械通气以及外周血单个核细胞 YAP、STAT3 mRNA 表达水平是脓毒症患者短期预后的影响因素 ($P<0.05$)。外周血单个核细胞 YAP、STAT3 mRNA 联合检测预测脓毒症患者短期预后的曲线下面积为 0.845,高于两指标单独检测的 0.623、0.687。**结论:**脓毒症患者短期预后的影响因素包括年龄、APACHE II 评分、机械通气以及合并基础疾病等,联合检测外周血单个核细胞 YAP、STAT3 mRNA 表达对脓毒症患者短期预后具有一定预测价值。

关键词:脓毒症;影响因素;短期预后;信号转导子和转录激活子 3;Yes 相关蛋白

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Influencing Factors of Short-Term Prognosis in Patients with Sepsis and the Predictive Value of YAP Combined with STAT3*

LIANG Han¹, ZHUANG Cheng-jun², ZHANG Qian¹, NIU Chang¹, REN Feng^{1Δ}

(1 Department of Clinical Laboratory, The Second Affiliated Hospital of Dalian Medical University, Liaoning, Dalian, 116027, China;

2 Department of Critical Medicine, The Second Affiliated Hospital of Dalian Medical University, Liaoning, Dalian, 116027, China)

ABSTRACT Objective: To investigate the influencing factors of short-term prognosis in patients with sepsis and the predictive value of Yes-related protein (YAP) combined with signal transduction and transcription activator 3 (STAT3) messenger RNA (mRNA) detection. **Methods:** 131 patients with sepsis who were admitted to our hospital from March 2019 to January 2021 were selected. They were divided into death group and survival group according to the difference in prognosis at 28 days. The baseline data and the peripheral blood mononuclear cells YAP and STAT3 mRNA expression levels were compared between the two groups. Multivariate Logistic regression was used to analyze the influencing factors of short-term prognosis in patients with sepsis. In addition, the peripheral blood mononuclear cells YAP and STAT3 mRNA expression were analyzed by receiver operating characteristic (ROC) curve to predict the short-term prognosis of patients with sepsis. **Results:** The relative expressions of peripheral blood mononuclear cells YAP and STAT3 mRNA in the death group patients were higher than those in the survival group patients ($P<0.05$). The age in the death group was longer than that in the survival group, the hospital stay was shorter than that in the survival group, the APACHE II score was higher than that in the survival group, and the proportion of patients combined with basic diseases and mechanical ventilation were higher than those in the survival group, the differences were statistically significant ($P<0.05$). Multivariate Logistic regression analysis showed that age, APACHE II score, combined with basic diseases, mechanical ventilation and expression levels of peripheral blood mononuclear cells YAP and STAT3 mRNA were adverse factors for the short-term prognosis of patients with sepsis ($P<0.05$). The area under the curve of the combined detection of peripheral blood mononuclear cells YAP and STAT3 mRNA to predict the short-term prognosis of patients with sepsis was 0.845, which was higher than 0.623 and 0.687 detected by the two indexes alone. **Conclusions:** The influencing factors of the short-term prognosis of patients with sepsis include age, APACHE II score, mechanical ventilation and combined with diseases, etc. Combined detection of the mRNA expression of peripheral blood mononuclear cells YAP and STAT3 has certain predictive value for the short-term prognosis of patients with sepsis.

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作者简介:梁晗(1993-),女,硕士研究生,初级技师,研究方向:胃癌分子诊断,E-mail: hanliang931003@163.com

Δ 通讯作者:任峰(1987-),男,博士研究生,主管技师,研究方向:感染性疾病病原微生物耐药机制及分子诊断,E-mail: dyrenfeng@126.com

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前言

脓毒症是指一组宿主对感染反应失调导致的危及生命安全的器官功能障碍综合症,是引起患者死亡的重要原因^[1,2]。中老年脓毒症患者的死亡率约 30%~40%,而感染性休克患者的死亡率高达 50%以上^[3]。因此,明确脓毒症患者短期预后的影响因素以及寻找灵敏度、特异度均较高的生物标志物对脓毒症早期预后进行预测一直是临床研究的热点^[4-6]。Yes 相关蛋白(YAP)属于转录辅激活因子,可通过和多种蛋白质的作用,继而促进影响细胞存活、增殖以及趋化的靶基因表达,属于细胞中 Hippo 信号转导通路的关键性分子,在炎症反应以及感染过程起着关键的调控效应,可能在脓毒症的发生、发展过程中发挥了重要作用^[7,8]。另有研究报道显示,信号转导子和转录激活子 3(STAT3)在脓毒症患者中存在异常表达,其可通过调控促炎因子以及抑炎因子的表达,直接作用于炎症信号传导通路其他重要分子等途径,间接参与脓毒症的发生、发展过程^[9,10]。鉴于此,本文通过研究脓毒症患者短期预后的影响因素及外周血单个核细胞 YAP、STAT3 信使 RNA(mRNA)表达的预测价值,旨在为临床治疗提供数据支持,现作以下报道。

1 资料与方法

1.1 一般资料

选择我院 2019 年 3 月~2021 年 1 月收治的 131 例脓毒症患者。其中男性 87 例,女性 44 例;年龄 28~87 岁,平均(60.68±11.37)岁。纳入标准:(1)均与脓毒症 3.0^[11]相关诊断标准相符;(2)年龄>18 岁;(3)入组前尚未接受相关治疗;(4)临床资料完整。排除标准:(1)合并免疫系统疾病、血液系统疾病或(和)恶性肿瘤者;(2)心、肝、肾等重要脏器功能严重不全者;(3)妊娠期或哺乳期女性;(4)意识障碍或合并精神疾病者;(5)研究期间因故退出或失访者。本研究符合《世界医学协会赫尔辛基宣言》相关要求。

1.2 研究方法

(1)外周血单个核细胞 YAP、STAT3 mRNA 表达水平检测:所有患者均于确诊 6 h 内采集静脉血 5 mL,置入 EDTA 抗

凝管抗凝,加入 RNA 稳定剂保存,放置于 -80℃ 冰箱中保存待测。采用 TRIzol 法进行淋巴细胞总 RNA 的提取,获取少量 RNA 溶液,以紫外分光光度计检测波长 260 以及 280 nm 的吸光度值,且以两者比值≥1.8 作为合格样品的标准。借助 TaKaRa PrimScript 逆转录试剂盒完成 cDNA 的获取。根据 GenBank 所提供的基因序列,分别设计引物。其中 YAP mRNA 上游引物序列为:5'-GATTGTGGTCGTATTGGGCGC-3'。下游引物序列为:5'-GTTGCTGCTGGTTGGAGTTG-3'。STAT3 mRNA 上游引物序列为:5'-CAGCAGCTTGACACACGGTA-3'。下游引物序列为:5'-AAACACCAAAGTGGCATGTGA-3'。根据相关试剂盒以及定量 PCR 仪说明书进行反应,相关参数设置如下:95℃ 30 s 预变性,95℃ 5 s 变性,60℃ 30 s 退火,70℃ 25 s 延伸,共 40 个循环。目的基因的相对表达量采用 $2^{-\Delta\Delta C_T}$ 进行表示。(2)根据 28 d 生存预后情况将所有患者分成死亡组 30 例和生存组 101 例。(3)基线资料采集:通过医院的病历系统对所有患者的基线资料进行统计、记录,内容包括:①性别;②年龄;③是否合并糖尿病、冠心病等基础疾病;④住院时间;⑤机械通气与否;⑥血液制品使用与否;⑦血管活性药物使用与否;⑧全身炎症反应综合征(SIRS)阳性例数;⑨急性生理与慢性健康评分系统 II(APACHE II)评分^[11]。其中 APACHE II 评分在患者确诊时进行评定。

1.3 统计学方法

以 SPSS 22.0 软件分析本研究数据。分析前先进行正态性与方差齐性检验,呈正态分布且具备方差齐性的计量资料以($\bar{x} \pm s$)表示,采用 t 检验。计数资料以[例(%)]表示,进行 χ^2 检验。脓毒症患者短期预后的影响因素采用多因素 Logistic 回归分析。通过受试者工作特征(ROC)曲线分析外周血单个核细胞 YAP、STAT3 mRNA 表达预测脓毒症患者短期预后的效能。 $P<0.05$ 表示差异有统计学意义。

2 结果

2.1 两组外周血单个核细胞 YAP、STAT3 mRNA 表达水平对比

死亡组患者的外周血单个核细胞 YAP、STAT3 mRNA 相对表达量均高于生存组患者($P<0.05$)。见表 1。

表 1 两组外周血单个核细胞 YAP、STAT3 mRNA 表达水平对比($\bar{x} \pm s$)

Table 1 Comparison of expression levels of peripheral blood mononuclear cells YAP and STAT3 mRNA between the two groups($\bar{x} \pm s$)

Groups	n	YAP mRNA	STAT3 mRNA
Death group	30	1.57±0.27	2.12±0.31
Survival group	101	1.37±0.21	1.78±0.23
t	-	4.277	6.535
P	-	0.000	0.000

2.2 两组基线资料对比

死亡组年龄大于生存组,住院时间短于生存组,APACHE II 评分高于生存组,合并基础疾病、机械通气的患者比例高于

生存组,差异均有统计学意义($P<0.05$);而两组在性别比例、使用血液制品与否、使用血管活性药物与否、SIRS 阳性比例方面差异无统计学意义($P>0.05$)。见表 2。

表 2 两组基线资料对比
Table 2 Comparison of baseline data between the two groups

Items	Death group(n=30)	Survival group(n=101)	χ^2/t	P
Gender(male/female)	19/11	68/33	0.074	0.785
Age($\bar{x} \pm s$, years)	67.37 $\pm$ 12.30	58.69 $\pm$ 10.03	3.956	0.000
Combined with basic diseases(n)	22(73.33%)	47(46.53%)	7.142	0.008
Hospital stay($\bar{x} \pm s$, d)	12.34 $\pm$ 2.34	16.58 $\pm$ 2.55	8.123	0.000
Mechanical ventilation(n)	18(60.00%)	34(33.66%)	7.108	0.008
Use of blood products(n)	14(46.67%)	31(30.69%)	2.617	0.106
Use of vasoactive drugs(n)	20(66.67%)	48(47.52%)	3.395	0.065
SIRS positive(n)	20(66.67%)	57(56.44%)	0.999	0.317
APACHE II score($\bar{x} \pm s$, scores)	21.72 $\pm$ 3.24	12.78 $\pm$ 1.68	20.265	0.000

2.3 脓毒症患者短期预后影响因素的多因素 Logistic 回归分析

以脓毒症短期预后为因变量,赋值:生存=0,死亡=1。以表 1 和表 2 差异有统计学意义的因素作为自变量,赋值如下:外周血单个核细胞 YAP、STAT3 mRNA 相对表达量、年龄、住院时间、APACHE II 评分均为原值输入;合并基础疾病=1,未合

并基础疾病=0;机械通气=1,无机械通气=0。经多因素 Logistic 回归分析可得:年龄、APACHE II 评分、合并基础疾病、机械通气以及外周血单个核细胞 YAP、STAT3 mRNA 表达水平是脓毒症患者短期预后的影响因素($P<0.05$),见表 3。

表 3 脓毒症患者短期预后影响因素的多因素 Logistic 回归分析
Table 3 Multivariate Logistic regression analysis of influencing factors of short-term prognosis in patients with sepsis

Factors	β	S.E	Wald χ^2	OR	P	95%CI
Constant term	-2.305	0.359	7.203	-	0.002	-
YAP mRNA	1.015	0.477	12.305	2.783	0.000	1.421~5.203
STAT3 mRNA	2.746	0.412	14.283	2.801	0.000	1.594~4.295
Age	1.485	0.489	6.242	1.304	0.019	1.034~2.015
Hospital stay	1.034	0.104	1.304	1.013	0.126	0.934~1.426
APACHE II score	2.105	0.512	7.289	1.578	0.012	1.189~2.412
Combined with basic diseases	1.879	0.289	9.189	2.019	0.001	1.435~3.182
Mechanical ventilation	3.279	0.378	8.201	1.893	0.004	1.245~2.893

2.4 外周血单个核细胞 YAP、STAT3 mRNA 表达预测脓毒症患者短期预后的效能

经 ROC 曲线分析可得:外周血单个核细胞 YAP、STAT3

mRNA 联合检测预测脓毒症患者短期预后的曲线下面积、灵敏度、特异度均高于两项指标单独检测。见表 4、图 1。

表 4 外周血单个核细胞 YAP、STAT3 mRNA 表达预测脓毒症患者短期预后的效能

Table 4 Efficacy of peripheral blood mononuclear cells YAP and STAT3 mRNA expression in predicting short-term prognosis of patients with sepsis

Indexes	Area under the curve	95%CI	Threshold	Sensitivity(%)	Specificity(%)	Jordan index
YAP mRNA	0.623	0.529~0.723	1.75	66.83	59.12	0.260
STAT3 mRNA	0.687	0.612~0.792	2.51	71.29	64.55	0.358
Two items combination	0.845	0.749~0.950	-	86.23	82.10	0.683

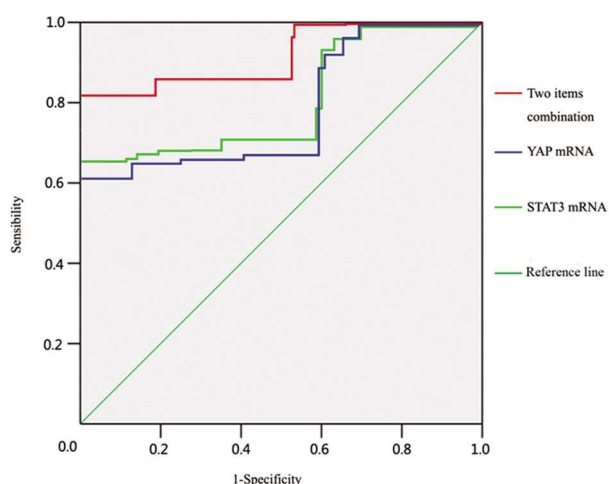


图1 外周血单个核细胞 YAP、STAT3 mRNA 表达预测脓毒症患者短期预后的 ROC 曲线

Fig.1 ROC curve of peripheral blood mononuclear cells YAP and STAT3 mRNA expression in predicting short-term prognosis in patients with sepsis

3 讨论

脓毒症是目前危急重症医学临床救治工作中所面临的重要挑战,亦是感染致死的主要原因。尽管医疗水平不断发展,新的诊疗方案以及药物层出不穷,但是脓毒症的病死率仍居高不下,是广大医务工作者亟待解决的重要问题之一^[12-14]。因此,明确脓毒症预后转归的相关影响因素以及有效预测标志物具有极其重要的临床意义。其中 YAP 是近年来新发现的 Hippo 信号通路重要下游效应物,其主要和非受体酪氨酸激酶 YES 的 SH3 片段结合,继而起到生物学效应,在细胞增殖、分化、趋化以及凋亡等过程中起着关键性作用,且在炎症调控过程中亦扮演着至关重要的角色^[15-17]。而脓毒症的病情发展与炎症反应存在着紧密联系,YAP 可能参与了脓毒症的发生、发展过程。STAT3 属于细胞内调控炎症的关键信号通路,在脓毒症发生、发展过程中发挥着至关重要的作用^[18-20]。迄今为止,关于上述两项指标应用于预测脓毒症短期预后的研究鲜见报道,具有一定的临床研究价值。

本文结果发现,死亡组年龄大于生存组,APACHE II 评分高于生存组,合并基础疾病、机械通气的患者比例高于生存组,且经多因素 Logistic 回归分析发现:年龄、APACHE II 评分、合并基础疾病、机械通气是脓毒症患者短期预后的影响因素。分析其原因主要是随着年龄的不断增长,患者机体抵抗力以及免疫力均出现不同程度的下降,不利于疾病的救治,因此预后往往不良^[21,22]。APACHE II 评分是临床上广泛用以反映机体状态的工具,该评分越高预示病情越重,状态越差,临床治疗难度较大,预后欠佳^[23,24]。而机械通气属于有创治疗手段,在治疗的同时会对患者造成一定程度的创伤,继而不利于疾病转归。同时,接受机械通气患者往往病情相对严重,预后势必欠佳。合并基础疾病患者往往受多种疾病的共同影响,从而可能出现更为明显的症状以及器官功能障碍,进一步对预后转归造成负面影响^[25,26]。此外,死亡组外周血单个核细胞 YAP、STAT3 mRNA 相对表达量均高于生存组。且经多因素 Logistic 回归分析发现:

外周血单个核细胞 YAP、STAT3 mRNA 表达水平较高是脓毒症患者短期预后的不利影响因素。原因在于 YAP 属于血管内皮细胞活化以及炎症的重要调控剂,炎症因子可诱导内皮细胞 YAP 的高表达,因此 YAP 的水平升高可反映机体炎症反应的加剧,患者病情加重^[27,28]。STAT3 的异常激活会导致大量炎症介质的合成、释放,进一步加剧患者感染症状,对患者预后产生不利影响^[29,30]。此外,本文 ROC 曲线分析结果显示,外周血单个核细胞 YAP、STAT3 mRNA 联合检测预测脓毒症患者短期预后的曲线下面积、灵敏度、特异度均高于上述两项指标单独检测。提示该两指标对脓毒症患者的短期预后具有较好的预测价值。分析原因,两项指标联合检测,可为临床预后的预测提供更为全面的依据,进一步达到提高预测效能的目的。

综上所述,与脓毒症患者短期预后有关的影响因素有年龄、APACHE II 评分、机械通气以及合并基础疾病,联合检测外周血单个核细胞 YAP、STAT3 mRNA 表达水平在预测脓毒症患者短期预后方面具有一定的价值。

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