

感染性心内膜炎患者外周血中性粒细胞外诱捕网水平与T细胞水平表达和预后的相关性研究

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摘要:目的 探讨感染性心内膜炎(infective endocarditis, IE)患者外周血中性粒细胞外诱捕网(neutrophil extracellular trap nets, NETs)水平与T细胞水平表达和预后的相关性。方法 选取2018年11月~2021年2月在青岛阜外心血管病医院治疗的53例IE患者作为IE组,选取同期进行体检的50例健康人群,作为对照组。比较两组血浆NETs水平和T细胞表达水平之间的差异,采用Pearson相关性检验分析血浆NETs水平和T细胞水平表达的相关性。根据IE患者生存情况分为存活组(29例)和死亡组(24例),采用受试者工作特征曲线(ROC曲线)分析血浆NETs水平对IE患者死亡的预测价值。结果 IE组患者cf-DNA/NETs($465.15 \pm 146.38 \mu\text{g/L}$), WBC($16.14 \pm 5.36 \times 10^9/\text{L}$), NEUT($75.42 \pm 10.25\%$), hs-CRP($39.38 \pm 10.75\text{g/L}$), CD3⁺($66.23 \pm 6.74\%$), CD4⁺($44.35 \pm 4.26\%$)和CD4⁺/CD8⁺(1.65 ± 0.43)水平均显著高于对照组[$135.76 \pm 37.52 \mu\text{g/L}$, (6.24 ± 1.53) $\times 10^9/\text{L}$, ($62.28 \pm 6.45\%$), $2.37 \pm 1.04\text{g/L}$, ($54.21 \pm 5.13\%$), ($35.14 \pm 3.52\%$), 1.34 ± 0.33],差异有统计学意义($t=18.093, 11.036, 7.352, 22.960, 9.505, 10.298, 5.289$, 均 $P < 0.01$)。血清Alb($35.38 \pm 10.75\text{g/L}$ vs $42.15 \pm 9.78 \text{g/L}$)和CD8⁺水平[($23.75 \pm 3.68\%$) vs ($26.75 \pm 3.66\%$)]显著低于对照组,差异有统计学意义($t=-4.039, -4.961$, 均 $P < 0.01$)。IE死亡组cf-DNA/NETs水平显著高于存活组($611.46 \pm 102.15 \mu\text{g/L}$ vs $407.53 \pm 76.49 \mu\text{g/L}$),差异均有统计学意义($t=7.007, P < 0.01$)。血浆cf-DNA/NETs水平与CD8⁺水平、患者预后不良呈正相关($r=0.282, 0.352$, 均 $P < 0.05$),与CD3⁺, CD4⁺和CD4⁺/CD8⁺水平呈负相关($r=-0.424, -0.535, -0.328$, 均 $P < 0.05$)。ROC曲线分析NETs预测IE患者死亡的曲线下面积为0.736(95%CI: 0.684 ~ 0.829, $P < 0.01$)。结论 感染性心内膜炎患者血浆NETs水平显著升高,血浆NETs水平与T细胞水平表达及患者预后不良显著相关,对预测IE患者死亡有一定临床价值。

关键词:感染性心内膜炎;中性粒细胞外诱捕网;T细胞

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Correlation between the Level of Peripheral Blood Neutrophil Extracellular Trap Nets and T Cell Expression and Prognosis in Patients with Infective Endocarditis

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Abstract: Objective To investigate the correlation between the level of peripheral blood neutrophil extracellular trap nets (NETs) and T cell expression and prognosis in patients with infective endocarditis (IE). **Methods** 53 patients with IE treated in Qingdao Fuwai Cardiovascular Hospital from November 2018 to February 2021 were selected as IE group, and 50 healthy people who underwent physical examination in the hospital during the same period were selected as control group. Plasma NETs levels and T cell expression levels were measured and compared between the two groups. Pearson correlation test was used to analyze the correlation between plasma NETs level and T cell level expression. According to the survival of IE patients, the patients were divided into the survival group (29 cases) and the death group (24 cases). Receiver operating characteristic curve (ROC curve) was used to analyze the predictive value of plasma NETs levels for death in IE patients. **Results** The levels of cf-DNA/NETs ($465.15 \pm 146.38 \mu\text{g/L}$), WBC ($16.14 \pm 5.36 \times 10^9/\text{L}$), NEUT ($75.42 \pm 10.25\%$), hs-CRP ($39.38 \pm 10.75\text{g/L}$), CD3⁺ ($66.23 \pm 6.74\%$), CD4⁺ ($44.35 \pm 4.26\%$) and CD4⁺/CD8⁺ (1.65 ± 0.43) in IE group were significantly higher than those in control group [$135.76 \pm 37.52 \mu\text{g/L}$, (6.24 ± 1.53) $\times 10^9/\text{L}$, ($62.28 \pm 6.45\%$), $2.37 \pm 1.04\text{g/L}$, ($54.21 \pm 5.13\%$), ($35.14 \pm 3.52\%$), 1.34 ± 0.33], difference was statistically significant ($t=18.093, 11.036, 7.352, 22.960, 9.505, 10.298, 5.289$, all $P < 0.01$). Serum Alb ($35.38 \pm 10.75\text{g/L}$ vs $42.15 \pm 9.78 \text{g/L}$) and CD8⁺ level [($23.75 \pm 3.68\%$) vs ($26.75 \pm 3.66\%$)] were significantly lower than control group, difference was statistically significant ($t=-4.039, -4.961$, all $P < 0.01$). IE death group cf-DNA/NETs level was significantly higher than survival group ($611.46 \pm 102.15 \mu\text{g/L}$ vs $407.53 \pm 76.49 \mu\text{g/L}$), difference was statistically significant ($t=7.007, P < 0.01$). Plasma cf-DNA/NETs level was positively correlated with CD8⁺ level and poor prognosis ($r=0.282, 0.352$, all $P < 0.05$), negatively correlated with CD3⁺, CD4⁺ and CD4⁺/CD8⁺ level ($r=-0.424, -0.535, -0.328$, all $P < 0.05$). ROC curve analysis showed that the area under the curve of NETs predicting IE patient death was 0.736 (95%CI: 0.684 ~ 0.829, $P < 0.01$). **Conclusion** The plasma NETs level of patients with infective endocarditis was significantly elevated, and the plasma NETs level was significantly correlated with T cell level expression and poor prognosis, which had certain clinical value for predicting the death of IE patients.

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3.52)%, 1.34 ± 0.33], the differences were statistically significant ($t=18.093, 11.036, 7.352, 22.960, 9.505, 10.298, 5.289$, all $P < 0.01$). Serum Alb (35.38 ± 10.75 g/L vs 42.15 ± 9.78 g/L) and $CD8^+[(23.75 \pm 3.68)\% \text{ vs } (26.75 \pm 3.66)\%]$ levels were significantly lower than control group, the differences were statistically significant ($t=-4.039, -4.961$, all $P < 0.01$). The cf-DNA/NETs level in IE death group was significantly higher than that in IE survival group ($611.46 \pm 102.15 \mu\text{g/L}$ vs $407.53 \pm 76.49 \mu\text{g/L}$), the difference was statistically significant ($t=7.007, P < 0.01$). Plasma cf-DNA/NETs levels were positively correlated with $CD8^+$ and poor prognosis in IE group ($r=0.282, 0.352$, all $P < 0.05$), and negatively correlated with $CD3^+, CD4^+$ and $CD4^+/CD8^+$ ($r=-0.424, -0.535, -0.328$, all $P < 0.05$). The ROC curve analysis showed that the area under the curve for NETs to predict death in IE patients was 0.736 (95%CI: 0.684 ~ 0.829, $P < 0.01$). **Conclusion** Plasma NETs was significantly increased in patients with infective endocarditis. plasma NETs level was significantly correlated with T cell level expression and poor prognosis, which has certain clinical value in predicting death in patients with IE.

Keywords: infective endocarditis; neutrophil extracellular trap nets; T cell

感染性心内膜炎 (infective endocarditis, IE) 是致病微生物经血路直接侵犯到患者心脏瓣膜、心内膜及大动脉内膜所致的炎症性疾病, 多发于先天性心脏病、风湿性心脏病及免疫力低下人群^[1-2]。感染、炎症等可激活机体免疫系统, 产生细胞因子, 中性粒细胞是天然免疫中数量最多、反应最快的细胞, 在感染性疾病中扮演重要角色。当病原体感染时, 中性粒细胞可通过吞噬、脱颗粒, 产生中性粒细胞外诱捕网 (neutrophil extracellular trap nets, NETs) 来攻击入侵的病原体, 另外中性粒细胞也参与适应性免疫, 可作为抗原提呈细胞向 T 细胞提呈抗原, 从而间接调控 T 细胞免疫^[3-4]。NETs 是活化的中性粒细胞释放的可限制病原体扩散的胞外纤维, 除能够抑制病原体生长与定植外, 有研究发现, 病原体可在 NETs 中存活, 且会对内皮细胞造成损伤, 表明 NETs 的释放也有促进病原的致病作用^[5]。目前 NETs 在系统性红斑狼疮^[6]、类风湿关节炎^[7]、糖尿病^[8]、肿瘤^[9]等疾病多有报道, 但在 IE 患者中 NETs 水平变化未见报道。本研究旨在观察 IE 患者外周血 NETs 水平变化, 并探讨其与 T 细胞水平表达和患者预后的相关性。

1 材料与方法

1.1 研究对象 选取 2018 年 11 月 ~ 2021 年 2 月在青岛阜外心血管病医院治疗的 53 例 IE 患者作为 IE 组, 其中男性 32 例, 女性 21 例; 年龄 18~76 (56.54 ± 13.43) 岁; 其中 8 例无基础心脏疾病, 18 例非风湿性心脏病, 14 例先天性心脏病, 7 例风湿性心脏病, 4 例人工瓣膜植入, 2 例心脏起搏器植入。纳入标准: ①临床症状及生化指标符合 IE 诊断标准^[10]; ②两次血培养阳性; ③经超声心动图确诊; ④患者知情同意。排除标准: ①非 IE 患者; ②并发其他感染性疾病; ③并发免疫系统疾病者; ④并发恶性肿瘤者; ⑤并发血液系统疾病者; ⑥并发认知功能障碍者; ⑦妊娠及哺乳期妇女。另选取同期进行体检的 50 例健康人群作为对照组, 其中男性 25 例, 女性 25 例, 年龄 18~75 (55.32 ± 12.35) 岁。

两组性别、年龄比较, 差异无统计学意义 ($\chi^2=1.121, P=0.290$; $t=-0.098, P=0.922$), 具有可比性。本研究经青岛阜外心血管病医院医学伦理委员会批准。

1.2 仪器与试剂 高速离心机 (Heraeus Fresco 21), Fluoroskan 荧光酶标仪 (美国 Thermo Fisher Scientific 公司); Pico Green 荧光染料 (德国 Leukocare AG 公司); 流式细胞仪 (BD-FACS Calibur) 及配套试剂 (美国 BD 公司); BC-5390 血细胞分析仪 (深圳迈瑞生物医疗公司); PHILIPS iE33 多普勒超声诊断仪 (上海欧启电子科技有限公司)。

1.3 方法

1.3.1 资料收集及生化指标测定: 收集 IE 患者和对照组的一般临床资料, 包括性别、年龄、病因, 采用血细胞分析仪测定外周血白细胞 (white blood cell, WBC) 计数, 中性粒细胞 (neutrophil, NEUT) 比例等指标。采用超声心动图检测患者左心室舒张期末内径 (left ventricular end diastolic diameter, LVEDD)、左心室射血分数 (left ventricular ejection fraction, LVEF) 等。

1.3.2 外周血游离 DNA/中性粒细胞胞外诱捕网陷阱 (cf-DNA/NETs) 水平和 T 细胞水平表达检测: IE 患者于入院次日, 对照组于体检当日采集空腹肘静脉血各 6 ml, 置于 EDTA 真空采血管中, 室温静置 10 min 后进行离心 (3000r/min , 10 min), 取上层血浆, -80°C 保存备用。室温解冻血浆样本, 取 $100 \mu\text{l}$ 血浆注入血培养瓶, 加入 PicoGreen 荧光染料避光孵育 5 min 后, 接种于 96 孔板内, 采用荧光酶标仪检测样本荧光值, 根据标准曲线计算 cf-DNA/NETs 水平。采用流式细胞仪检测 T 淋巴细胞亚群 $CD3^+, CD4^+, CD8^+$, 计算 $CD4^+/CD8^+$, 检测方法严格按照说明书操作。

1.4 统计学分析 采用 SPSS 22.0 软件进行统计学分析, 计数数据以 $n(\%)$ 表示, 组间比较采用 χ^2 检验, 计量数据符合正态分布以均数 \pm 标准差 ($\bar{x} \pm s$) 表示, 使用独立样本的 t 检验比较两组血浆 NETs 水平和 T 细胞表达水平之间的差异; 采用 Pearson

相关性检验分析 IE 患者血浆 NETs 水平与 T 细胞水平表达的相关性;采用受试者工作特征曲线(ROC 曲线)分析血浆 NETs 水平对 IE 患者死亡的预测价值, $P < 0.05$ 为差异具有统计学意义。

2 结果

2.1 两组患者生化指标及 T 细胞水平表达比较见表 1。IE 组患者 cf-DNA/NETs, WBC, NEUT,

hs-CRP, $CD3^+$, $CD4^+$ 和 $CD4^+/CD8^+$ 水平均显著高于对照组健康人群,差异具有统计学意义(均 $P < 0.01$);IE 患者血清 Alb 和 $CD8^+$ 水平显著低于对照组,差异具有统计学意义(均 $P < 0.01$);两组血红蛋白、LVEDD 和 LVEF 比较,差异均无统计学意义(均 $P > 0.05$)。

表 1 两组患者生化指标及 T 细胞水平表达比较 ($\bar{x} \pm s$)

项目	IE 组 ($n=53$)	对照组 ($n=50$)	t 值	P 值
cf-DNA/NETs($\mu\text{g/L}$)	465.15 \pm 146.38	135.76 \pm 37.52	18.093	0.000
WBC($\times 10^9/\text{L}$)	16.14 \pm 5.36	6.24 \pm 1.53	11.036	0.000
NEUT(%)	75.42 \pm 10.25	62.28 \pm 6.45	7.352	0.000
Hb(g/L)	138.45 \pm 12.51	142.56 \pm 13.23	-1.143	0.256
Alb(g/L)	35.38 \pm 10.75	42.15 \pm 9.78	-4.039	0.000
hs-CRP(g/L)	39.38 \pm 10.75	2.37 \pm 1.04	22.960	0.000
LVEDD(mm)	56.62 \pm 12.18	55.47 \pm 10.25	0.522	0.603
LVEF(%)	52.16 \pm 5.72	53.41 \pm 6.39	-1.850	0.067
$CD3^+$ (%)	66.23 \pm 6.74	54.21 \pm 5.13	9.505	0.000
$CD4^+$ (%)	44.35 \pm 4.26	35.14 \pm 3.52	10.298	0.000
$CD8^+$ (%)	23.75 \pm 3.68	26.75 \pm 3.66	-4.961	0.000
$CD4^+/CD8^+$	1.65 \pm 0.43	1.34 \pm 0.33	5.289	0.000

注:WBC:白细胞计数;NEUT:中性粒细胞;Hb:血红蛋白;Alb:清蛋白;hs-CRP:超敏 C-反应蛋白;LVEDD:左心室舒张期末内径;LVEF:左心室射血分数。

2.2 IE 患者 NETs 水平与 T 细胞水平表达及预后的相关性分析 根据 IE 患者预后情况分为存活组(29 例)和死亡组(24 例),死亡组患者 cf-DNA/NETs 水平为 $611.46 \pm 102.15 \mu\text{g/L}$,存活组患者 cf-DNA/NETs 水平为 $407.53 \pm 76.49 \mu\text{g/L}$,两组比较差异具有统计学意义($t=7.007$, $P < 0.01$)。Pearson 相关性分析显示:IE 患者血浆 cf-DNA/NETs 水平与 $CD8^+$ 水平和死亡呈正相关($r=0.282$, 0.352 , $P=0.041$, 0.048),与 $CD3^+$, $CD4^+$ 和 $CD4^+/CD8^+$ 呈负相关($r=-0.424$, -0.535 , -0.32 , $P=0.002$, 0.000 , 0.016)。

2.3 外周血 NETs 水平对预后的价值分析 见图 1。以 IE 患者入院治疗为研究起点,以患者痊愈出院、死亡或出现严重并发症为研究终点,绘制 ROC 曲线。结果显示,外周血 NETs 水平对预测 IE 死亡有参考意义($P < 0.05$)。NETs 预测 IE 患者死亡的曲线下面积为 0.736 (95%CI: 0.684~0.829, $P < 0.01$),预测敏感度、特异度分别为 81.29%, 75.35%。

3 讨论

感染性心内膜炎(IE)是死亡率高达 15%~20% 的感染性疾病,其典型生物学特征是赘生物的形成,赘生物主要由大小不等、形状不一的血小

板和纤维素团块组成,内含大量病原微生物。赘生物定植于受损的心瓣膜内膜(天然瓣膜 IE)或心内假体(假体 IE)上,不仅可造成瓣膜周围组织破坏,赘生物脱落还可导致血管栓塞、猝死及心力衰竭等^[11]。

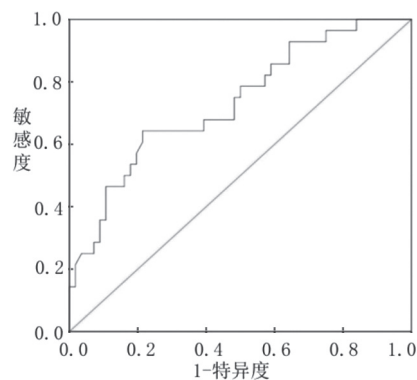


图 1 外周血 NETs 水平预测 IE 预后的 ROC 曲线

炎症反应是 IE 最基础、最关键的病理改变。病原菌的繁殖及内毒素的释放可激发机体白细胞、淋巴细胞、中性粒细胞等炎症细胞的释放以强化对病原菌的吞噬和清除能力^[12]。还可以刺激机体产生炎症反应,导致相关炎症指标迅速升高^[13]。本研究中 IE 组患者 WBC, NEUT, hs-CRP 等常规炎症指标水平显著高于对照组。中性粒细胞是宿主防御病

原体的第一道防线,能够通过趋化、吞噬、氧化应激、形成 NETs 等方式捕获和杀死微生物^[14]。NETs 是一种由染色质和颗粒肽结合形成的纤维网状结构,NETs 可被真菌、细菌、病毒等多种微生物激活,由中性粒细胞分泌并释放至胞外,从而固定和清除微生物,并激活其他免疫细胞、介导炎症反应^[15-16]。目前认为,NET 捕获、黏附病原体主要依赖于三维网状结构,而杀灭病原体依赖于抗菌蛋白^[17]。NETs 的形成是由致病菌在全身血液感染中诱导的,既往研究表明,NET 内容物可在组织感染部位含量显著升高。已有研究发现,在 IE 患者的脓毒性血栓,检测到 NETs^[18]。本研究分析 IE 患者外周血 NETs 水平,结果显示与健康人群相比,IE 患者外周血 NETs 水平显著升高,证实血浆 NETs 与感染相关。IE 患者死亡组 NETs 水平显著高于存活组,ROC 曲线结果显示,NETs 预测 IE 患者死亡的曲线下面积为 0.736,结果提示,外周血 NETs 水平与 IE 患者预后不良密切相关。

免疫功能的改变在 IE 患者中有重要作用,CD3⁺, CD4⁺, CD8⁺ 是重要的 T 淋巴细胞,其中 CD3⁺ 细胞水平代表机体整体细胞免疫状态^[19],CD4⁺ 主要发挥调节免疫应答的功能,通常被称为辅助性 T 淋巴细胞^[20],而 CD8⁺ 具有抑制免疫功能的作用,可抑制 CD4⁺ 细胞及 B 细胞功能,被称为抑制性 T 淋巴细胞^[21]。对 IE 患者外周血 T 淋巴细胞亚群各个指标进行检测,可较为准确地反映患者当时的免疫状态,本研究结果显示 IE 患者 CD3⁺, CD4⁺ 和 CD4⁺/CD8⁺ 水平均低于对照组,CD8⁺ 水平高于对照组 ($P < 0.05$),表明 IE 患者存在免疫功能降低。另外,研究发现 IE 患者外周血中 NETs 水平与 T 细胞表达水平相关,与 CD8⁺ 呈正相关 ($P < 0.05$),与 CD3⁺, CD4⁺ 和 CD4⁺/CD8⁺ 呈负相关 ($P < 0.05$)。这符合 NETs 为广义的致病性 DNA 复合物的定义,机体的炎症状态与 NETs 水平相关。

综上所述,本研究结果表明 IE 患者外周血 NETs 水平显著升高,其水平变化与 T 细胞表达水平密切相关,与 IE 患者预后不良显著相关。但本研究也有一定的局限性,首先,研究样本量较少,由此可能带来结果的偏倚,还需要大样本、多中心研究以验证本结果的准确性。另外,本研究未剖析 IE 患者外周血 NETs 水平升高具体机制,这些仍需要进一步研究证实。

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