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· 临床研究 ·

血清降钙素原检测对早期诊断肝衰竭合并感染的临床意义*

杨 凡 焦方舟 李 汛 王鲁文 龚作炯[△]

(武汉大学人民医院感染科 湖北 武汉 430060)

摘要 目的:探讨血清降钙素原(PCT)检测在肝衰竭合并感染早期诊断中的临床意义。**方法:**选择 2014 年 3 月至 2017 年 3 月我院收治的由病毒性肝炎导致的肝衰竭患者 102 例为研究对象,根据有无感染分为感染组(75 例)和非感染组(27 例),采用干式免疫荧光法检测其血清 PCT 水平,并检测两组患者白细胞(WBC)水平、C 反应蛋白(CRP)水平、中性粒细胞百分比(N%),进行全身炎症反应综合征(SIRS)评分,采用多因素 Logistic 回归模型分析 PCT、WBC、CRP、N%水平和 SIRS 评分对肝衰竭合并感染的预测价值大小,绘制受试者工作特征曲线(ROC 曲线)评价 PCT、WBC、CRP、N%水平和 SIRS 评分对肝衰竭合并感染的诊断价值。**结果:**感染组 PCT、WBC、N%、CRP 水平和 SIRS 评分均高于非感染组($P<0.05$);不同感染部位患者 WBC、N%、CRP 水平和 SIRS 评分比较差异不明显($P>0.05$);多部位感染患者血清 PCT 水平均高于其他单部位感染患者($P<0.05$);多因素 Logistic 回归分析显示,PCT 和 N%水平是肝衰竭合并感染的独立危险因素($P<0.05$);PCT、N%、CRP、WBC 水平和 SIRS 评分诊断肝衰竭合并感染的 ROC 曲线下面积(AUC)值依次为 0.916、0.763、0.752、0.746、0.682,PCT 诊断肝衰竭合并感染的 AUC 值分别与 N%、CRP、WBC 和 SIRS 评分比较差异均有统计学意义($Z=3.518、3.672、4.103、5.106,P<0.05$)。**结论:**肝衰竭合并感染患者血清 PCT 水平明显升高,PCT 对肝衰竭合并感染的诊断价值优于 WBC、CRP、N%和 SIRS 评分等传统实验室指标。

关键词:肝衰竭;降钙素原;感染;早期诊断;临床意义

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Clinical Significance of Serum Procalcitonin Detection in Early Diagnosis of Liver Failure Complicate with Infection*

YANG Fan, JIAO Fang-zhou, LI Xun, WANG Lu-wen, GONG Zuo-jiong[△]

(Department of Infectious Disease, Renmin Hospital of Wuhan University, Wuhan, Hubei, 430060, China)

ABSTRACT Objective: To explore the clinical significance of serum procalcitonin (PCT) detection in the early diagnosis of liver failure complicate with infection. **Methods:** 102 patients with liver failure caused by viral hepatitis who were treated in our hospital from March 2014 to March 2017 were selected as the object, the patients were divided into infection group (75 cases) and non infection group (27 cases) according to whether or not they were infected, the level of serum PCT was detected by dry immunofluorescence method, the levels of white blood cell (WBC), C reactive protein (CRP) and neutrophil percentage (N%) were detected in the two groups, systemic inflammatory response syndrome (SIRS) score was performed, multivariate logistic regression was used to analyze the predictive value of PCT, WBC, CRP, N% levels and SIRS scores in the diagnosis of liver failure complicated with infection, the receiver operating characteristic curve (ROC curve) was drawn to evaluate the diagnostic value of PCT, WBC, CRP, N% levels and SIRS scores in patients with liver failure complicated with infection. **Results:** The levels of PCT, WBC, N%, CRP and SIRS scores in the infection group were higher than those in the non infection group ($P<0.05$). There were no significant differences in WBC, N%, CRP levels and SIRS scores between different infection sites ($P>0.05$). Serum PCT levels in patients with multiple site infections were higher than those in other single site infections ($P<0.05$). Multivariate Logistic regression analysis showed that the levels of PCT and N% were independent risk factors for liver failure complicated with infection ($P<0.05$). The area under the ROC curve (AUC) of PCT, N%, CRP, WBC levels and SIRS scores were 0.916, 0.763, 0.752, 0.746 and 0.682 respectively for diagnosis of liver failure complicated with infection. The differences were statistically significant between the AUC of PCT diagnosis of liver failure complicated with infection and the N%, CRP, WBC levels and SIRS scores ($Z=3.518, 3.672, 4.103, 5.106, P<0.05$). **Conclusion:** The level of serum PCT in patients with liver failure complicate with infection is obviously higher, and the diagnostic value of PCT for liver failure complicate with infection is superior to the traditional laboratory indexes such as WBC, CRP, N% and SIRS score.

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作者简介:杨凡(1986-),男,博士,住院医师,从事慢性肝病的防治方面的研究,E-mail:mnhgigif@163.com

[△] 通讯作者:龚作炯(1962-),男,博士,主任医师,从事慢性肝病的防治方面的研究,E-mail:fgbfo@163.com

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前言

我国是病毒性肝炎大国,其中慢性乙型肝炎及慢性丙型肝炎患者病情管理不当易造成肝功能衰竭,如急性肝功能衰竭、慢性肝功能衰竭、慢加急性肝功能衰竭,肝衰竭患者由于肝功能受损严重,存在免疫功能紊乱,极易发生多种并发症,其中感染是较为常见的并发症之一^[1-3]。既往研究表明^[4-6],肝衰竭患者并发感染可引起肝细胞再生困难、持续性高黄疸,是导致患者病情进一步恶化的重要因素之一,同时也是导致肝衰竭患者死亡的重要原因。因此,积极预防或治疗感染对提高肝衰竭患者预后积极意义。积极有效的治疗需以明确的诊断为依据,临床上对肝衰竭合并感染的诊断主要根据患者的临床症状、体征、实验室检查(包括血象、腹水细胞学、腹水培养及腹水生化等)和影像学检查等,但以上各种方法通常需要联合检查,方便性欠佳,在肝衰竭合并感染的早期诊断中应用局限性非常明显^[7-9]。降钙素原(Procalcitonin, PCT)是一种无激素活性的降钙素前肽物质,健康机体血清中 PCT 浓度非常低(<0.1 ng/ml)且非常稳定,在内毒素等因子的诱导下,2~3h 开始增加,已被证实为是一个可以诊断和监测细菌性炎症疾病感染的参数^[10-12]。然而,关于血清中 PCT 对肝衰竭合并感染的诊断价值的研究较少,因此本文分析通过检测血清中 PCT 对肝衰竭合并感染早期诊断的意义,以期临床提供参考依据。

1 资料和方法

1.1 一般资料

选择 2014 年 3 月至 2017 年 3 月我院收治的由病毒性肝炎(乙型肝炎或丙型肝炎)导致的肝衰竭患者 102 例为研究对象。纳入标准:(1)所有患者均符合 2012 年版《肝衰竭诊治指南》中关于肝衰竭的诊断标准^[13];(2)一般资料完整,完成涵盖本研究所需的检查项目者。排除标准:(1)合并其他疾病可能影响血清 PCT 水平者;(2)近期(1 周内)服用药物可能影响血清 PCT 水平者;(3)存在器官移植病史者。腹膜炎(SBP)的诊断依据 2010 年欧洲肝病学会肝硬化腹水、自发性细菌性腹膜炎临床实践指南^[14],肺部感染及尿道感染有相应的临床检测证据,诊断标准参考卫生部 2001 版医院感染诊断标准^[15],根据上述标准,将合并感染的 75 例患者归入感染组,未合并感染的 27 例患者归入非感染组。感染组:男 63 例,女 12 例;年龄 22~75 岁,平均(44.67 ± 9.68)岁;引起肝衰竭的基础病:慢性乙型肝炎 45 例,乙型肝炎肝硬化 24 例,丙型肝炎肝硬化 6 例;肝衰竭类型:慢加急性肝衰竭 43 例,慢性肝衰竭 25 例,急性肝衰竭 7 例;感染部位:单纯肺部感染 16 例,单纯腹膜感染 21 例,单纯尿道感染 3 例,多部位感染 35 例。非感染组:男 22 例,女 5 例;年龄 21~73 岁,平均(43.58 ± 9.13)岁;引起肝衰竭的基础病:慢性乙型肝炎 16 例,乙型肝炎肝硬化 10 例,丙型肝炎肝硬化 1 例;肝衰竭类型:慢加急性肝衰竭 14 例,慢性肝衰竭 9 例,急性肝衰竭 4 例。两组患者的性别、年龄、基础病、肝衰竭类型等一

般资料比较差异无统计学意义($P>0.05$)。本研究经医院伦理委员会批准同意。

1.2 方法

两组患者均于入院后采集清晨空腹静脉血 5 mL,以 3000 r/min 离心 10 min,离心半径为 8 cm,取血清待测。采用干式免疫荧光法检测其血清 PCT 水平, $PCT \geq 0.5$ ng/mL 为阳性。采用武汉大学人民医院检验科全自动生化分析仪分析全血中白细胞(White blood cell, WBC)水平和中性粒细胞百分比(N%),WBC 参考值 $3.5 \sim 9.5 \times 10^9$ 个/L, N%参考值 40.0%~75.0%。采用胶乳增强免疫比浊法检测两组患者血清中 C 反应蛋白(CRP)水平,正常参考值 <10.0 ng/mL。所有患者均进行全身炎症反应综合征(SIRS)评分^[16],包括心率(HR)、体温(T)、WBC 和呼吸频率(RR)4 项,每项 0~4 分,总分 = 各项评分之和/4,得分越高提示病情越严重。

1.3 观察指标

(1)比较两组患者以及感染组不同感染部位患者 PCT、WBC、N%、CRP 水平和 SIRS 评分情况。(2)以发生感染或不发生感染为因变量,以 PCT、WBC、N%、CRP 水平和 SIRS 评分为自变量,采用多因素 Logistic 回归模型分析 PCT、WBC、N%、CRP 和 SIRS 在预测肝衰竭合并感染中的作用大小。(3)绘制 ROC 曲线,分析 PCT、WBC、N%、CRP 和 SIRS 对肝衰竭合并感染的诊断价值,灵敏度 = 真阳性例数 / (真阳性例数 + 假阴性例数) * 100%,特异度 = 真阴性例数 / (真阴性例数 + 假阳性例数) * 100%,阳性预测值 = 真阳性例数 / (真阳性例数 + 假阳性例数) * 100%,阴性预测值 = 真阴性例数 / (真阴性例数 + 假阴性例数) * 100%。

1.4 统计学方法

研究中的数据资料均采用 SPSS21.0 统计学软件进行分析,采用均数 $\pm$ 标准差($\bar{x} \pm s$)描述,两组比较采用独立样本 χ^2 检验,多组比较采用方差分析;计数资料采用率(%)表示,组间比较采用 χ^2 检验;ROC 曲线下面积(AUC)比较采用秩和检验,以 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 两组患者 PCT、WBC、N%、CRP 水平和 SIRS 评分比较

感染组 PCT、WBC、N%、CRP 水平和 SIRS 评分均高于非感染组,差异有统计学意义($P<0.05$)。详见表 1。

2.2 不同感染部位患者 PCT、WBC、N%、CRP 水平和 SIRS 评分比较

不同感染部位患者 WBC、N%、CRP 水平和 SIRS 评分比较差异无统计学意义($P>0.05$),而不同感染部位患者 PCT 比较差异有统计学意义($P<0.05$);多部位感染患者血清 PCT 水平平均高于其他单部位感染患者,差异有统计学意义($P<0.05$)。详见表 2。

2.3 多因素 Logistic 回归分析

多因素 Logistic 回归分析显示,PCT 和 N%水平是肝衰

竭合并感染的独立危险因素($P<0.05$),而 WBC、CRP 水平和 SIRS 评分对肝衰竭合并感染的预测价值较小($P>0.05$)。详见表 3。

SIRS 评分对肝衰竭合并感染的预测价值较小($P>0.05$)。详见表 3。

表 1 两组 PCT、WBC、N%、CRP 水平和 SIRS 评分比较($\bar{x}\pm s$)

Table 1 Comparison of the PCT, WBC, N% levels and SIRS scores between the two groups($\bar{x}\pm s$)

Groups	n	PCT(ng/ml)	WBC($\times 10^9$ /individual/L)	N%	CRP(ng/mL)	SIRS(score)
Infection group	75	2.12 $\pm$ 0.78	9.27 $\pm$ 2.13	75.92 $\pm$ 11.36	21.37 $\pm$ 5.62	2.78 $\pm$ 0.49
Non infection group	27	0.37 $\pm$ 0.25	6.85 $\pm$ 1.76	63.18 $\pm$ 9.63	11.78 $\pm$ 3.54	0.55 $\pm$ 0.07
t	-	6.572	2.964	4.365	6.478	4.276
P	-	0.000	0.002	0.000	0.000	0.000

表 2 不同感染部位患者 PCT、WBC、N%、CRP 水平和 SIRS 评分比较($\bar{x}\pm s$)

Table 2 Comparison of the PCT, WBC, N% levels and SIRS scores in patients with different site of infection($\bar{x}\pm s$)

Site of infection	n	PCT(ng/ml)	WBC($\times 10^9$ /individual/L)	N%	CRP(ng/mL)	SIRS(score)
Lung	16	1.01 $\pm$ 0.46*	8.72 $\pm$ 2.04	74.82 $\pm$ 10.18	22.16 $\pm$ 5.32	2.66 $\pm$ 0.74
Peritoneum	21	1.37 $\pm$ 0.58*	9.18 $\pm$ 1.96	76.11 $\pm$ 9.75	21.76 $\pm$ 4.54	2.38 $\pm$ 0.52
Urethra	3	1.41 $\pm$ 0.92*	8.84 $\pm$ 1.11	74.71 $\pm$ 5.36	20.41 $\pm$ 2.38	2.76 $\pm$ 0.43
Multiple sites	35	2.53 $\pm$ 0.96	9.42 $\pm$ 2.25	76.34 $\pm$ 9.61	23.49 $\pm$ 6.18	2.95 $\pm$ 1.12
F	-	2.485	0.683	0.369	0.437	1.032
P	-	0.008	0.542	0.814	0.725	0.207

Note: compared with multiple sites, * $P<0.05$.

表 3 各指标对肝衰竭合并感染的预测价值 Logistic 回归分析

Table 3 Logistic regression analysis of predictive value of various indexes for liver failure complicated with infection

Variables	β	SE	Wald	P	OR	95%CI
PCT	1.549	0.784	17.546	0.000	21.476	3.784~25.476
N%	0.026	0.045	7.384	0.002	4.653	1.059~6.384
SIRS score	0.713	0.136	1.906	0.185	0.812	0.993~1.418
WBC	0.118	0.124	1.738	0.153	0.785	0.762~1.137
CRP	0.145	0.043	1.582	0.137	0.743	0.582~1.416

2.4 PCT、WBC、N%、CRP 水平和 SIRS 评分对肝衰竭合并感染的诊断价值

PCT 诊断肝衰竭合并感染的 AUC 值最大(0.916),其他依次为 N%(0.763)、CRP (0.752)、WBC (0.746) 和 SIRS 评分(0.682),详见图 1。PCT 诊断肝衰竭合并感染的 AUC 值分别与

N%、CRP、WBC 和 SIRS 评分比较,差异均有统计学意义($Z=3.518, 3.672, 4.103, 5.106, P<0.05$)。当约登指数最大时,PCT、N%、SIRS 评分、CRP 和 WBC 诊断肝衰竭合并感染的灵敏度、特异度、阳性预测值、阴性预测值。见表 4。

表 4 各指标对肝衰竭合并感染的诊断价值

Table 4 The diagnostic value of various indexes in liver failure complicated with infection

Indexs	Youden index	Critical value	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value(%)
PCT	0.762	≥ 0.60 ng/mL	93.23	82.97	87.30	90.70
N%	0.368	$\geq 75\%$	65.93	80.85	78.60	69.40
CRP	0.413	≥ 13.0 mg/L	82.46	69.57	71.28	73.76
WBC($\times 10^9$ /L)	0.420	$\geq 10 \times 10^9$ /L	53.92	87.23	76.91	52.48
SIRS score	0.211	≥ 2 scores	43.67	56.74	69.78	65.49

3 讨论

相关报告显示^[17],肝衰竭患者的病死率约 60%~90%。由于肝衰竭患者存在肝脏补体合成能力下降、细胞(中性粒细胞和

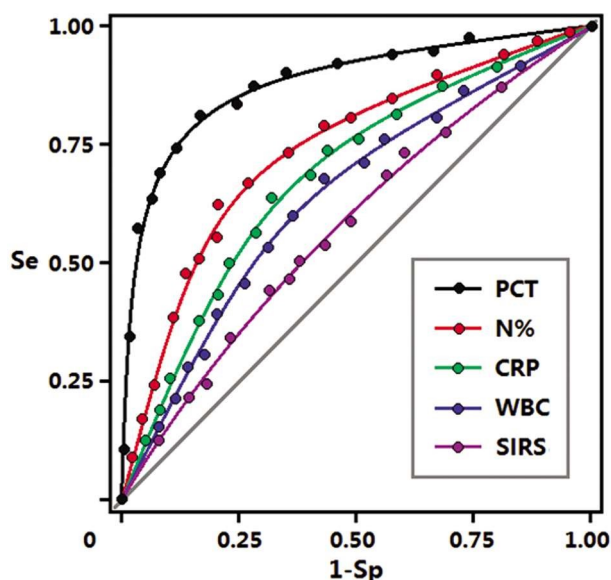


图1 PCT、N%、CRP、WBC及SIRS诊断肝衰竭合并感染的ROC曲线
Fig.1 PCT, N%, CRP, WBC and SIRS in diagnosis of liver failure complicated with infection of ROC curve

Kupffer 细胞)吞噬功能受损、肠道菌群异位等情况,并发感染的机会增加,相关报道显示^[18]肝衰竭合并感染的发生率高达80%左右。本研究中102例患者,合并感染的75例,占73.53%。肝衰竭并发感染不仅使患者病情加重,还严重影响了患者的生活质量,甚至威胁到患者的生命安全,因此早期明确诊断予以有效干预在肝衰竭的整个治疗过程中意义重大。N%、CRP、WBC是实验室常用的诊断感染的指标,但其诊断肝衰竭合并感染的敏感性较低,容易发生漏诊情况,漏诊了约30%^[19,20]。已有研究表明^[21],肝衰竭合并感染患者的SIRS评分显著高于肺感染患者及健康人群,但仅依靠SIRS评分对感染进行诊断,其敏感性低,诊断价值有限。PCT是一种新型的生物标志物,被广泛应用于一般人群感染的早期诊断、治疗监测及预后评估中^[22-24],但应用于肝衰竭合并感染的诊断的研究较少,其诊断价值尚待进一步证实。

本研究显示,感染组患者PCT、WBC、N%、CRP水平和SIRS评分均高于非感染组($P<0.05$),提示肝衰竭合并感染患者PCT、WBC、N%、CRP水平和SIRS评分均显著升高,可能是由于:PCT是一种无激素活性的糖蛋白,由116个氨基酸残基构成,相对分子量为13kD,半衰期25~30h,健康机体中PCT含量极低且稳定性良好^[25-27]。在感染及炎症反应等病理状态下,机体肿瘤坏死因子(TNF- α)、白细胞介素-1(IL-1)、白细胞介素-2(IL-2)等多糖和败血症因子水平升高,而TNF- α 、IL-1、IL-2等会诱导PCT产生,进而导致PCT浓度升高^[28]。不同部位感染患者WBC、N%、CRP水平和SIRS评分比较差异不明显($P>0.05$);但多部位感染患者血清PCT水平均高于其他各单部位感染患者($P<0.05$),提示常规实验室指标无法反应感染的真实情况,而血清PCT水平有助于判断肝衰竭合并感染的具体情况。多因素Logistic回归分析显示,PCT和N%水平是肝衰竭合并感染的独立危险因素($P<0.05$),且PCT对肝衰竭合并感染的预测作用大于N%($PPCT<PN\%$)。ROC曲线分析显示,PCT诊断肝衰竭合并感染的AUC值最大为0.916,说明

PCT对肝衰竭合并感染具有较高的诊断价值;N%、CRP、WBC、SIRS评分诊断肝衰竭合并感染的AUC值依次为0.763、0.752、0.746、0.682,说明N%、CRP、WBC、SIRS评分对肝衰竭合并感染具有中等诊断价值;PCT诊断肝衰竭合并感染的AUC值显著大于N%、CRP、WBC和SIRS评分($P<0.05$)。以上结果表明,较传统的实验室指标及SIRS评分而言,PCT对肝衰竭合并感染具有更高的诊断价值。需要指出的是,目前临床及多数学术研究中,通常以 $PCT\geq 0.5\text{ ng/mL}$ 为诊断感染的截断值^[29,30]。本研究则显示,当约登指数最大时(即诊断效果最佳时),PCT的截断值为 $\geq 0.6\text{ ng/mL}$,说明在PCT诊断肝衰竭合并感染时,截断值不能以正常人群的参考值为标准,其原因是因为肝衰竭患者本身就存在肠源性内毒素血症,较正常人群而言肝衰竭患者血清PCT水平较高,因而血清PCT基础水平较高。另外,本研究显示不同部位感染患者血清PCT水平比较差异不明显($P>0.05$),可能因为消化道感染的病例数很少,导致结果发生偏移,说服力不强,还有待于进一步研究。

综上所述,血清PCT对肝衰竭合并感染的早期诊断价值优于N%、CRP、WBC等传统指标及SIRS评分,临床上采用血清PCT诊断肝衰竭合并感染中,建议以 $PCT\geq 0.6\text{ ng/mL}$ 截断值,提高诊断效能,减少漏诊及误诊率。

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