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不同严重程度急性胰腺炎患者血清中 PCT、hs-CRP、TNF- α 水平及临床意义 *

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摘要 目的:探讨降钙素原(PCT)、超敏 C 反应蛋白(hs-CRP)、肿瘤坏死因子- α (TNF- α)在轻症、重症急性胰腺炎(AP)患者血清中的表达水平及临床意义。**方法:**选取我院在 2016 年 1 月~2018 年 7 月期间收治的 AP 患者 108 例进行研究,并记为 AP 组,其中轻症急性胰腺炎(MAP)患者 58 例纳入 MAP 组,重症急性胰腺炎(SAP)患者 50 例纳入 SAP 组,另选取同期在我院进行体检的 50 例健康体检者作为对照组。AP 组患者于入院第 1 d、3 d、7 d、14 d 采用酶联免疫吸附试验(ELISA)检测血清中 PCT、hs-CRP、TNF- α 水平,对照组仅在体检时检测血清中 PCT、hs-CRP、TNF- α 水平。将 AP 组患者分为全身炎症反应综合征(SIRS)组和非 SIRS 组,比较 SIRS 组和非 SIRS 组血清中 PCT、hs-CRP、TNF- α 水平的差异。采用 Spearman 相关性分析 AP 患者入院第 1 d 的血清 PCT、hs-CRP、TNF- α 水平的相关性。**结果:**与对照组比较,AP 组患者入院第 1 d 血清 PCT、hs-CRP、TNF- α 水平升高($P<0.05$)。入院第 1 d、3 d、7 d、14 d 时 SAP 组患者的血清 PCT、hs-CRP、TNF- α 水平均高于 MAP 组患者($P<0.05$),SAP 组患者各指标在第 3 d 达到峰值,此后依次降低,而 MAP 组患者各指标随入院时间的延长持续降低。SIRS 组患者入院第 1 d 的血清 PCT 水平高于非 SIRS 组患者($P<0.05$),而两组血清 hs-CRP、TNF- α 水平比较差异无统计学意义($P>0.05$)。经 Spearman 相关性分析显示,AP 患者入院第 1 d 的血清 PCT、hs-CRP、TNF- α 水平互为正相关关系($P<0.05$)。**结论:**AP 患者血清中 PCT、hs-CRP、TNF- α 水平偏高,与病情严重程度密切相关,且三指标之间呈正相关,检测血清 PCT、hs-CRP、TNF- α 可为该病诊断、病情评估、疗效评估提供依据。

关键词:急性胰腺炎;降钙素原;超敏 C 反应蛋白;肿瘤坏死因子- α ;病情严重程度;相关性

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Expression and Clinical Significance of Serum PCT, hs-CRP and TNF- α in Patients with Different Severity of Acute Pancreatitis*

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ABSTRACT Objective: To investigate the expression and significance of serum procalcitonin (PCT), hypersensitive C-reactive protein (hs-CRP) and tumor necrosis factor- α (TNF- α) in mild and severe acute pancreatitis (AP). **Methods:** 108 patients with AP who were treated in our hospital from January 2016 to July 2018 were selected, and they were recorded as AP group. Among them, 58 patients with mild acute pancreatitis (MAP) were included in MAP group, 50 patients with severe acute pancreatitis (SAP) were included in SAP group. Another 50 healthy persons who underwent physical examination in our hospital during the same period were selected as control group. The levels of serum PCT, hs-CRP and TNF- α were detected by enzyme-linked immunosorbent assay (ELISA) at the 1 d, 3 d, 7 d and 14 d after admission in AP group. The levels of serum PCT, hs-CRP and TNF- α in the control group were measured only at the time of physical examination. Patients in AP group were divided into systemic inflammatory response syndrome (SIRS) group and non SIRS group. The differences of serum PCT, hs-CRP and TNF- α levels between the two groups were compared. Spearman correlation analysis was used to analyze the correlation of PCT, hs-CRP and TNF- α levels in patients with AP at 1 d of admission. **Results:** The levels of serum PCT, hs-CRP and TNF- α at 1 d of admission in AP group were higher than those in the control group ($P<0.05$). The levels of serum PCT, hs-CRP and TNF- α in SAP group were higher than those in MAP group at 1 d, 3 d, 7 d and 14 d after admission ($P<0.05$). The indexes of SAP group were reached the peak at 3 d, and then they were decreased in turn. After treatment, the indexes of MAP group were continued to decrease with the increase of admission time. The level of serum PCT in group SIRS at 1 d of admission was higher than that in non SIRS group ($P<0.05$). There was no significant difference in the levels of serum hs-CRP and TNF- α between the two groups ($P>0.05$). Spearman correlation analysis showed that the levels of serum PCT, hs-CRP and TNF- α in patients with AP at 1 d of admission were positively correlated with each other ($P<0.05$). **Conclusion:** The levels of serum PCT, hs-CRP and TNF- α in patients with AP were highly expressed. They are closely related to the severity of the disease, and there is a positive correlation between the three indicators, detection of serum PCT, hs-CRP and TNF- α can provide a basis for the diagnosis of the disease, disease judgment, efficacy evaluation.

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前言

急性胰腺炎(Acute pancreatitis, AP)是消化系统常见的一种急腹症之一,该病是由多种因素导致的胰蛋白酶在胰腺内被激活,并对胰腺组织自身产生作用,从而引起胰腺组织的消化、出血、水肿甚至坏死等炎症现象,同时炎症将导致患者出现剧烈腹痛、发热、恶心呕吐、休克等临床症状,严重威胁患者的生命健康和生活质量^[1-3]。该病可根据病情严重程度分为轻症和重症,其中重症急性胰腺炎(Severe acute pancreatitis, SAP)起病急促,病情进展迅速,若治疗不善会有一定的致死率^[4,5]。部分轻症急性胰腺炎(Mild acute pancreatitis, MAP)患者随着病情的进展也可能转化成 SAP^[6]。另外,AP 患者由于免疫力低下易受外界感染因素的影响,从而出现全身炎症反应综合征(Systemic inflammatory response syndrome, SIRS),进一步加重患者的病情,同时 SIRS 的出现也会促使 MAP 患者病情加重,进而转化为 SAP^[7,8]。因此,尽早地确诊和治疗 SAP、MAP 患者,对于患者取得良好的预后具有重要意义。近年来,关于各种细胞因子与 AP 病情发生发展的相关性研究报道越来越多,有多种细胞因子可能参与了 AP 的发病过程,而肿瘤坏死因子- α (Tumor necrosis factor- α , TNF- α)、降钙素原(Procalcitonin, PCT)、超敏 C 反应蛋白(Hypersensitive C reactive protein, hs-CRP)在机体的炎症反应和免疫调节中起到重要作用,可能参与了 AP 的发病过程^[9-11]。因此,本研究通过对 SAP、MAP 患者在不同治疗时期的血清中 PCT、hs-CRP、TNF- α 水平进行测定,以期 AP 的诊断、病情预测等提供参考依据。

1 资料与方法

1.1 临床资料

选取 108 例于我院在 2016 年 1 月~2018 年 7 月期间接受治疗的 AP 患者进行研究,纳入 AP 组。按病情严重程度将 MAP 患者 58 例纳入 MAP 组, SAP 患者 50 例纳入 SAP 组,纳入标准^[12]:(1)MAP、SAP 患者符合中华医学会消化病分会制定的《中国急性胰腺炎诊治指南》中的诊断标准,并结合患者临床症状、血清淀粉酶、多普勒超声等技术手段进行确诊。(2)所有患者发病到入院接受诊治时间不超过 24 h,且均为首次发病。(3)患者经超声或腹部 CT 检查显示有胰腺肿大现象;(4)签署知情同意书者。排除标准:(1)慢性胰腺炎患者;(2)并发全身恶性肿瘤患者;(3)严重心肝肾功能不全、自身免疫性疾病患者。其中 MAP 组男性 32 例,女性 26 例,患者年龄 35~71 岁,平均(57.82 $\pm$ 5.39)岁,其中酒精型 13 例、特发型 19 例、饮食型 13 例、混合型 13 例;SAP 组男性 27 例,女性 23 例,患者年龄 37~69 岁,平均(56.95 $\pm$ 5.43)岁,其中酒精型 9 例、特发型 16 例、饮食型 13 例、混合型 12 例。另取同期在我院进行体检的健康志愿者 50 例为对照组,其中男性 26 例,女性 24 例,年龄 33~67 岁,平均(55.82 $\pm$ 7.84)岁。三组基线资料比较无统计学

差异($P>0.05$)。研究方案经我院伦理学委员会批准。

1.2 检测方法

108 例患者在入院确诊为 AP 后,给予禁食、胃肠减压以及奥美拉唑、生长抑素、乌司他丁、抗生素等药物治疗,并采用补充营养液的方式进行营养支持治疗。入院第 1 d、3 d、7 d、14 d 采用酶联免疫吸附试验(Enzyme-linked immunosorbent assay, ELISA)检测 SAP、MAP 患者血清中 PCT、hs-CRP、TNF- α 水平,具体方法为采集患者空腹静脉血 5 mL,采用 SC-3616 型高速离心机(安徽中科中佳科学仪器有限公司)进行离心,3000 rpm/min,10 min 后分离得到血清样品,采用罗氏 Cobase 601 仪器以及配套的北京新产业试剂检测 PCT,采用西门子 BNII 特殊蛋白分析仪以及配套的西门子 C 反应蛋白试剂检测 hs-CRP,采用贝克曼 FC500 流式细胞分析仪检测 TNF- α ,操作步骤严格按照说明书要求进行。对照组受试者仅在体检时采集静脉血,按上述相同方法检测血清中 PCT、hs-CRP、TNF- α 水平。

1.3 SIRS 诊断标准^[13]

进一步将 AP 组患者按 SIRS 诊断标准分为 SIRS 组($n=43$)和非 SIRS 组($n=65$),对比两组入院第 1 d 的各指标水平,SIRS 诊断标准为:① 患者肛温 $>38^{\circ}\text{C}$ 或 $<36^{\circ}\text{C}$;② 心率 >90 次/min;③ 呼吸 >20 次/min 或 $\text{PCO}_2<32.33$ mmHg;④ 白血细胞计数 $>12\times 10^9/\text{L}$ 或 $<4\times 10^9/\text{L}$ ($>12000/\mu\text{L}$ 或 $<4000/\mu\text{L}$ 或未成熟粒细胞 $>10\%$)。当患者满足以上 4 条中的 2 条即可确诊为 SIRS。

1.4 统计学方法

选择 SPSS21.0 统计软件实施数据的统计分析,采用($\bar{x}\pm s$)表示计量资料,实施 t 检验,采用[n(%)]表示计数资料,实施 χ^2 检验,相关性分析采用 Spearman 相关性检验,以 $\alpha=0.05$ 为检验水准。

2 结果

2.1 AP 组与对照组血清 PCT、hs-CRP、TNF- α 水平比较

与对照组比较,AP 组患者入院第 1 d 血清 PCT、hs-CRP、TNF- α 水平升高($P<0.05$),见表 1。

2.2 SAP 组和 MAP 组入院后不同时间血清 PCT、hs-CRP、TNF- α 水平比较

入院第 1 d、3 d、7 d、14 d 时 SAP 组患者的血清 PCT、hs-CRP、TNF- α 均高于 MAP 组患者($P<0.05$),经治疗后 SAP 组患者各项指标在第 3 d 达到峰值,此后依次降低,MAP 组患者各指标随入院时间的延长持续降低,见表 2。

2.3 SIRS 组与非 SIRS 组入院第 1 d 的血清 PCT、hs-CRP、TNF- α 水平比较

入院后第 1 d, SIRS 组患者的血清 PCT 水平高于非 SIRS 组患者($P<0.05$),而两组血清 hs-CRP、TNF- α 水平比较差异无统计学意义($P>0.05$),见表 3。

表 1 AP 组与对照组血清 PCT、hs-CRP、TNF- α 水平比较($\bar{x} \pm s$)Table 1 Comparison of serum PCT, hs-CRP and TNF- α levels between AP group and control group($\bar{x} \pm s$)

Groups	n	PCT(ng/mL)	hs-CRP(ng/mL)	TNF- α (pg/mL)
AP group	108	3.33 $\pm$ 1.95	21.57 $\pm$ 8.48	42.05 $\pm$ 12.30
Control group	50	0.40 $\pm$ 0.11	2.02 $\pm$ 0.36	12.05 $\pm$ 2.36
t	-	10.599	16.267	17.074
P	-	0.000	0.000	0.000

表 2 SAP 组和 MAP 组入院后不同时点血清 PCT、hs-CRP、TNF- α 水平比较($\bar{x} \pm s$)Table 2 Comparison of serum PCT, hs-CRP and TNF- α levels at different time points after admission between SAP group and MAP group($\bar{x} \pm s$)

Groups	n	Time	PCT(ng/mL)	hs-CRP(ng/mL)	TNF- α (pg/mL)
SAP group	50	1 d	4.31 $\pm$ 1.09*	25.37 $\pm$ 4.09*	48.93 $\pm$ 6.38*
		3 d	5.38 $\pm$ 1.22*	32.74 $\pm$ 3.21*	54.72 $\pm$ 5.40*
		7 d	3.02 $\pm$ 0.91*	20.60 $\pm$ 2.94*	30.27 $\pm$ 4.85*
		14 d	2.24 $\pm$ 0.67*	15.21 $\pm$ 2.57*	25.12 $\pm$ 3.36*
MAP group	50	1 d	2.48 $\pm$ 0.86	18.30 $\pm$ 3.09	36.11 $\pm$ 5.38
		3 d	1.87 $\pm$ 0.61	15.79 $\pm$ 2.91	28.38 $\pm$ 4.40
		7 d	1.54 $\pm$ 0.48	11.37 $\pm$ 2.64	19.09 $\pm$ 3.42
		14 d	1.08 $\pm$ 0.32	7.38 $\pm$ 1.96	14.89 $\pm$ 3.01

Note: comparison with corresponding time points in MAP group, * $P < 0.05$.

表 3 SIRS 组与非 SIRS 组血清 PCT、hs-CRP、TNF- α 水平比较($\bar{x} \pm s$)Table 3 Comparison of serum PCT, hs-CRP and TNF- α levels between SIRS group and non SIRS group($\bar{x} \pm s$)

Groups	n	PCT(ng/mL)	hs-CRP(ng/mL)	TNF- α (pg/mL)
SIRS group	43	4.28 $\pm$ 1.01	22.23 $\pm$ 8.41	42.91 $\pm$ 12.65
Non SIRS group	65	2.70 $\pm$ 0.74	21.13 $\pm$ 7.89	41.48 $\pm$ 11.15
t	-	9.377	0.691	0.618
P	-	0.000	0.491	0.538

2.4 相关性分析

经 Spearman 相关性分析显示,AP 患者入院第 1 d 的血清 PCT 与 hs-CRP、TNF- α 水平呈正相关($r=0.459, 0.313, P=0.000, 0.032$),血清 hs-CRP 与 TNF- α 水平也呈正相关($r=0.441, P=0.008$)。

3 讨论

近年来 AP 患者的发病率逐渐升高,对患者的危害性进一步增强,若不及时诊断和进行妥善有效的治疗干预,将影响其预后效果^[14,15]。在 AP 患者中,MAP 通常发病程度轻微,具有自限性,加以治疗后均可康复,而 SAP 患者通常症状较为严重,还可能并发 SIRS 等感染性症状,对患者的危害性更大,若治疗不及时可能造成患者死亡^[16]。因此,尽早的诊断和有效的治疗对于 SAP 患者至关重要,可积极改善预后效果。目前对于 AP 的发病原因尚不完全清楚,较为认可的观点是 AP 的发生与机体胰蛋白酶的过多分泌、相关细胞因子释放增多等因素有关^[17,18]。有报道显示^[19],AP 发病后在很短的时间内胰腺间质内的促炎性细胞因子即开始大量释放,引起全身性的炎症反应,并加重对胰腺的损伤,此项研究初步表明了各项炎性细胞因子参与了

AP 疾病的发生和进展过程。因此,分析探讨参与 AP 发病的细胞炎症因子,并将其作为 AP 发病的特异性指标,对于 AP 的诊断及病情评估有着重要意义。在众多细胞炎症因子中,PCT、hs-CRP、TNF- α 是备受人们关注的焦点,本研究中也着重考察了这 3 个指标在 AP 疾病中的临床意义。

在本研究中,入院第 1 d AP 组患者与对照组相比,PCT、hs-CRP、TNF- α 水平显著升高,初步表明此 3 项指标对 AP 发病早期具有一定的诊断价值。在 AP 患者中,对 MAP 和 SAP 患者进行为期 14 d 的各项指标的取样检测,结果显示 SAP 组患者在入院第 1 d、3 d、7 d、14 d 时的 PCT、hs-CRP、TNF- α 水平均高于 MAP 组患者,且 AP 患者入院第 1 d 的 PCT 与 hs-CRP、TNF- α 水平互为正相关关系,表明 PCT、hs-CRP、TNF- α 水平与 AP 患者的病情程度有关。以上结果均表明了 PCT、hs-CRP、TNF- α 等细胞炎症因子参与了 AP 的发病和疾病进展过程。其中 PCT 为多个氨基酸缩合组成的糖蛋白,属于降钙素的前肽物质,主要由肝脏等合成分泌,其主要发挥抗炎调节的生物学功能。在健康人群体内,PCT 的含量处于较低水平,当机体出现感染或其他炎症反应时,其含量会急剧升高,同时还会引起人血促炎性因子的升高,而炎性因子又反作用诱导

PCT的合成,因此PCT作为一种次级炎症因子参与AP发病的级联反应^[20,21]。PCT在AP发病的早期即迅速升高,并可将MAP与SAP患者区分开,对AP病情严重程度判断有重要参考意义^[22,23]。hs-CRP是由机体受到外界刺激因素或组织损伤等炎症性刺激时肝细胞合成的急性相蛋白,AP患者由于机体的感染因素的存在,使其水平迅速升高,并逐步达到峰值,经治疗后机体炎症反应减轻,hs-CRP的合成与分泌减少,使得其水平值逐步下降并恢复正常^[24-26]。在MAP和SAP两组各时间点的hs-CRP比较中,均有差异性,表明hs-CRP水平与AP患者疾病程度有明显关系。TNF- α 是一种具有直接杀伤肿瘤细胞并对正常细胞无明显毒性的细胞因子,另外,其还参与了机体内的炎症反应,是继发性炎症反应的重要趋化因子^[27,28],因此在AP疾病发病和进展中发挥重要作用,且SAP组患者TNF- α 一直保持在较高的水平,均高于MAP组,表明了TNF- α 参与了AP的发生和发展过程^[29,30]。另外,本研究AP患者中SIRS组患者的PCT水平显著高于非SIRS组患者,而hs-CRP、TNF- α 比较差异无统计学意义,说明AP伴SIRS患者PCT水平较高。

综上所述,AP患者血清中PCT、hs-CRP、TNF- α 水平较高,在入院治疗后两组患者的各项指标水平均逐渐降低。血清中PCT、hs-CRP、TNF- α 水平与病情严重程度密切相关,因此,检测患者血清中PCT、hs-CRP、TNF- α 水平可为AP患者的疾病诊断、病情评估、疗效判断提供参考依据。

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