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炎症因子表达水平与重症急性胰腺炎预后及肠道屏障损伤的相关性*

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摘要 目的:探讨白细胞介素-6(IL-6)、降钙素原(PCT)、C反应蛋白(CRP)相关炎症因子表达水平对重症急性胰腺炎(SAP)预后的预测价值,并分析不同炎症因子表达与肠道屏障损伤的相关性。**方法:**选取我院2019年8月到2022年8月收治的60例SAP患者为研究对象,对所有患者进行28 d随访,将28 d内死亡的20例患者分为死亡组,将其余40例患者分为存活组,对比两组患者临床一般情况与IL-6、PCT、CRP相关炎症因子表达水平,并分析SAP预后影响的独立危险因素。随后将所有患者依照肠道屏障损伤情况进行分组,分为肠道屏障损伤组(n=42)与非肠道损伤组(n=18),对比两组患者IL-6、PCT、CRP表达水平,分析炎症因子表达水平与肠道屏障损伤的相关性,并绘制各指标诊断SAP肠道屏障损伤的ROC曲线,分析其预测肠道屏障损伤的灵敏度与特异度。**结果:**存活组与死亡组患者胰腺坏死、APACHE II评分、发生器官衰竭情况与IL-6、PCT、CRP表达水平对比差异显著($P<0.05$);PCT、CRP、APACHE II评分为重症胰腺炎患者的预后不良影响因素($P<0.05$);肠道屏障损伤组患者IL-6、PCT、CRP表达水平明显高于非肠道屏障损伤组($P<0.05$);Spearman相关分析结果显示:IL-6、PCT、CRP与肠道屏障损伤呈正相关($P<0.05$);ROC曲线分析显示:曲线下面积(AUC)从低到高依次为IL-6(0.631)、CRP(0.667)、PCT(0.671)、联合诊断(0.852)。血清IL-6、PCT、CRP的联合诊断的灵敏度与特异度明显高于血清IL-6、PCT、CRP单一诊断($P<0.05$)。**结论:**IL-6、PCT、CRP相关炎症因子表达水平可预测SAP患者预后情况,IL-6、PCT、CRP与SAP肠道屏障损伤呈正相关,且三者联合对SAP肠道屏障损伤的诊断具有重要价值。

关键词:炎症因子;SAP;肠道屏障损伤;灵敏度;特异度

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Correlation between the Expression of Inflammatory Factors and Prognosis of Severe Acute Pancreatitis and Intestinal Barrier Injury*

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ABSTRACT Objective: To explore the predictive value of the expression levels of interleukin-6 (IL-6), procalcitonin (PCT), C-reactive protein (CRP) - related inflammatory factors on the prognosis of severe acute pancreatitis (SAP), and to analyze the correlation between the expression of different inflammatory factors and intestinal barrier damage. **Methods:** 60 SAP patients admitted to our hospital from August 2019 to August 2022 were selected as the research objects. All patients were followed up for 28 days. 20 patients who died within 28 days were divided into death groups, and the remaining 40 patients were divided into survival groups. The clinical general conditions and the expression levels of IL-6, PCT and CRP related inflammatory factors of the two groups were compared, and the independent risk factors affecting the prognosis of SAP were analyzed. Subsequently, all patients were divided into intestinal barrier injury group (n=23) and non intestinal barrier injury group (n=37) according to the intestinal barrier injury. The expression levels of IL-6, PCT and CRP in the two groups were compared. Spearman correlation analysis was used to analyze the correlation between the expression level of inflammatory factors and intestinal barrier injury, and the ROC curve of each index in diagnosing SAP intestinal barrier injury was drawn, To analyze the sensitivity and specificity of predicting intestinal barrier injury. **Results:** There was difference in pancreatic necrosis, sapache II score, occurrence of organ failure and expression levels of IL-6, PCT and CRP between the survival group and the death group ($P<0.05$); PCT, CRP and sapache II scores were the poor prognostic factors in patients with severe pancreatitis ($P<0.05$); The expression levels of IL-6, PCT and CRP in the intestinal barrier injury group were higher than those in the non intestinal barrier injury group ($P<0.05$); Spearman correlation analysis showed that IL-6, PCT and CRP were positively correlated with intestinal barrier injury ($P<0.05$); ROC curve analysis showed that the area under the curve (AUC) from low to high was IL-6 (0.631), CRP (0.667), PCT (0.671) and combined diagnosis (0.852). The sensitivity and specificity of combined diagnosis of serum IL-6, PCT and

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CRP were higher than those of single diagnosis of serum IL-6, PCT and CRP ($P<0.05$). **Conclusion:** The expression levels of IL-6, PCT and CRP related inflammatory factors can predict the prognosis of SAP patients. IL-6, PCT and CRP are positively correlated with SAP intestinal barrier damage, and the combination of the three has important value in the diagnosis of SAP intestinal barrier damage.

Key words: Inflammatory factors; SAP; Intestinal barrier damage; Sensitivity; Specificity

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前言

重症胰腺炎属于急性胰腺炎的一种特殊类型,病情险恶,且并发症较多,死亡率较高^[1,2]。随着临床医学发展,虽然在重症胰腺炎的治疗上有了一定进展,但是因为重症胰腺炎的病因复杂,导致患者预后评估缺乏更准确的指标^[3]。当前临床上,对重症胰腺炎预后评估的公认指标为急性生理与慢性健康(Acute physiology and chronic health evaluation-II, APACHE II)评分,但因其评分方法存在一定局限性^[4]。另外,研究发现 SAP 的感染与肠道屏障损伤具有一定关系^[5]。完整肠道粘膜可以为患者机体形成一道屏障,避免肠道菌群进入到肠外血管,但是当肠道粘膜出现炎症因子过度释放或缺血缺氧后,会对肠道环境产生破坏,进而引发 SAP 的细胞凋亡^[6]。因此,为了分析重症胰腺炎患者是否出现肠道屏障损伤与预后评估指标,本文探讨了炎症因子表达水平与 SAP 预后及肠道屏障损伤的相关性。

1 资料与方法

1.1 一般资料

选取我院 2019 年 8 月到 2022 年 8 月收治的 60 例 SAP 患者作为研究对象。

入选标准:均符合 SAP 诊断标准^[7];对本研究知情并签署同意书;经我院伦理委员会批准。

排除标准:年龄<18 岁的患者;妊娠期或哺乳期女性。

依照患者的预后情况将其分为死亡组(患者自动出院后随访 28 天内死亡或住院期间死亡)和存活组(患者病症好转之后出院,且 28 天内存活)。

1.2 方法

所有患者均接受急性胰腺炎常规治疗,包括营养支持、止痛、加强监护以及液体复苏等。必要情况补充人血清蛋白,对呼吸衰竭的患者需要应用呼吸机进行辅助呼吸。

1.3 观察指标

(1)统计患者的发病原因、年龄、BMI、性别、是否出现胰腺坏死、是否出现器官衰竭以及预后情况等一般资料,记录两组患者的 APACHE II 评分和白蛋白-胆红素评分水平。其中 APACHE II 评分包括三部分分数越高表示患者病情越严重。

(2)检测患者入住 ICU 24 小时之内的白细胞介素-6(IL-6)、降钙素原(PCT)、C 反应蛋白(CRP)水平。

(3)患者入院后第二天对患者肠道屏障损伤情况进行评估,具体方法为:①腹水、血培养细菌阳性,但无明显病灶感染;②肠通透性增加;③血浆内毒素表达水平 >55.34 EU/L;④原发疾病基础上出现消化道出血、腹泻或便秘、腹胀、腹痛、肠鸣音减弱、不耐受食物等;⑤存在导致肠道屏障障碍的危重症疾病。经病理诊断发生肠道黏膜屏障功能障碍,且符合上述情况的患

者将纳入到肠道屏障损伤组,其余的将纳入非肠道屏障损伤组。

以肠道屏障损伤分级标准为 5 种:0 级为正常;1 级为出现轻微肠道粘膜损伤,绒毛顶端上皮脱落;2 级为中度损伤,部分黏膜隐窝破溃;3 级为严重损伤,大部分隐窝破溃;4 级为肠道腔壁坏死,黏膜下层与黏膜出现坏死;5 级为肠壁与肠道透壁均坏死,出现出血现象。

1.4 统计学方法

采取 SPSS 23.0 对分析,计数资料以(n/%)表示,进行 χ^2 检验;符计量资料用($\bar{x}\pm s$)表示,采用 t 检验;采用 Spearman 相关分析方法分析;采用 logistic 回归分析;并绘制受试者特征工作(ROC)曲线分析灵敏度与特异度;以 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 一般临床情况与炎症因子水平对比

存活组与死亡组患者胰腺坏死、APACHE II 评分、发生器官衰竭情况与 IL-6、PCT、CRP 表达水平对比差异显著($P<0.05$),如表 1 所示。

2.2 SAP 预后影响的独立危险因素分析

对差异指标进行赋值:IL-6 ≥ 52.52 为 0, <52.52 为 1; PCT ≥ 3.06 为 0, <3.06 为 1; CRP ≥ 98.24 为 1, <98.24 为 0;胰腺坏死:发生为 1,未发生为 0;器官衰竭:发生为 1,未发生为 0;APACHE II 评分 ≥ 6.54 为 1, <6.54 为 0。IL-6、PCT、CRP、APACHE II 评分为重症胰腺炎患者的预后不良影响因素($P<0.05$),如表 2 所示。

2.3 肠道屏障损伤组与非肠道屏障损伤组 IL-6、PCT、CRP 表达水平对比

肠道屏障损伤组患者 IL-6、PCT、CRP 表达水平明显高于非肠道屏障损伤组($P<0.05$),如表 3 所示。

2.4 IL-6、PCT、CRP 表达水平与肠道损伤的相关性

Spearman 相关分析结果显示:IL-6、PCT、CRP 与肠道屏障损伤呈正相关($P<0.05$),如表 4 所示。

2.5 IL-6、PCT、CRP 对肠道屏障损伤的诊断价值

ROC 曲线分析显示:曲线下面积(AUC)从低到高依次为 IL-6(0.631)、CRP(0.667)、PCT(0.671)、联合诊断(0.852)。血清 IL-6、PCT、CRP 的联合诊断的灵敏度与特异度明显高于血清 IL-6、PCT、CRP 单一诊断($P<0.05$)。见表 5、图 1 所示。

3 讨论

SAP 的发病机制虽无明确定论,但多数学者认为与细胞因子过度释放和胰酶激活具有一定关系^[8]。大量研究证明^[9,10], SAP 发病之后 15 min 会出现胰腺间质白细胞浸润激活现象,释放大量炎症细胞,促使全身性炎症反应,造成多器官功能综

表 1 生存组与死亡组的一般临床情况及炎症因子水平的比较

Table 1 Comparison of general clinical conditions and levels of inflammatory factors between survival group and death group

Category	Survival group (n=40)	Death group(n=20)	χ^2/t	P
Gender (cases)				
male	23	11	0.437	0.508
female	18	8		
Age (years)	53.29±3.42	53.30±3.57	0.013	0.99
BMI(kg/m ²)	23.14±2.34	23.19±2.29	0.095	0.925
Pancreatic necrosis (yes / no)	3/37	8/12	9.406	0.002
APACHE II	5.08±2.35	12.43±6.24	8.538	0.001
Organ failure (yes / no)	2/38	13/7	25.600	0.001
IL-6(pg/mL)	35.64±8.91	61.72±12.87	9.179	0.001
PCT(μg/L)	2.47±0.58	3.38±0.75	5.186	0.001
CRP(mg/L)	75.30±21.09	132.52±38.73	4.509	0.001

表 2 影响 SAP 预后的独立危险因素分析

Table 2 Analysis of independent risk factors affecting the prognosis of SAP

Factors	Parameter estimate	Standard error	Wald	P	OR	95% CI
IL-6	0.463	0.096	8.096	0.063	2.546	1.364~3.475
PCT	0.457	0.089	8.145	0.030	2.458	1.359~3.257
CRP	0.635	0.108	10.484	0.008	0.464	0.210~1.347
Pancreatic necrosis	0.464	0.105	8.484	0.216	2.774	1.876~4.010
Organ failure	0.847	0.304	13.274	0.124	0.747	0.314~1.249
APACHE II	0.465	0.081	6.413	0.015	1.287	0.562~2.453

表 3 肠屏障损伤组与非肠屏障损伤组 IL-6、PCT、CRP 表达水平的比较($\bar{x} \pm s$)

Table 3 Comparison of IL-6, PCT and CRP expression levels between intestinal barrier injury group and non intestinal barrier injury group ($\bar{x} \pm s$)

Groups	n	IL-6(pg/mL)	PCT(μg/L)	CRP(mg/L)
Intestinal barrier injury group	42	57.54±12.42	3.46±0.24	81.25±23.25
Non intestinal barrier injury group	18	38.86±11.47	2.12±0.38	125.25±32.12
t	-	5.458	16.506	5.970
P	-	0.001	0.001	0.001

表 4 IL-6、PCT、CRP 表达水平与肠屏障损伤的相关性

Table 4 Correlation between IL-6, PCT, CRP expression levels and intestinal barrier damage

Indexs	Intestinal barrier damage	
	r	P
IL-6	0.586	0.013
PCT	0.579	0.018
CRP	0.374	0.009

合征,这也是加重 SAP 病情和死亡率的重要原因。因此,分析炎症因子和 SAP 的关系成为临床研究的热点内容。IL-6 属于多功能细胞因子的一种,在机体遭受细菌感染后炎症介质对淋巴细胞和单核细胞产生刺激,释放 IL-6^[11]。因此,可应用 IL-6 区分慢性期和急性期炎症^[12]。PCT 属于一种由 116 个氨基酸所组成的相关无激活性糖蛋白,属于降钙素前提,正常情况下人体

内含有的 PCT 水平极低,但具体生物学作用尚无确切定论^[13]。正常生理状态下是由位于甲状腺 C 细胞的 CALC-1 基因所合成,通过特异性肽链内切酶裂解成为钙抑肽、降钙素和 N-PCT,且 PCT 的半衰期为 25-30 小时^[14-16]。研究发现^[17],降钙素原和降钙素相比血清浓度较高、代谢快、生物活性高,临床检测更容易,而且不依赖肾脏排泄。CRP 可激活补体和加强吞噬细胞的

表 5 IL-6、PCT、CRP 对肠屏障损伤的诊断价值

Table 5 diagnostic value of IL-6, PCT and CRP for intestinal barrier injury

Indexs	AUC	Cutoff point	Sensitivity(%)	Specificity(%)
IL-6	0.631	1.27	51.87	55.47
CRP	0.667	9.97	48.03	67.53
PCT	0.671	2.37	62.58	86.32
Joint diagnosis	0.852	3.65	87.36	93.56

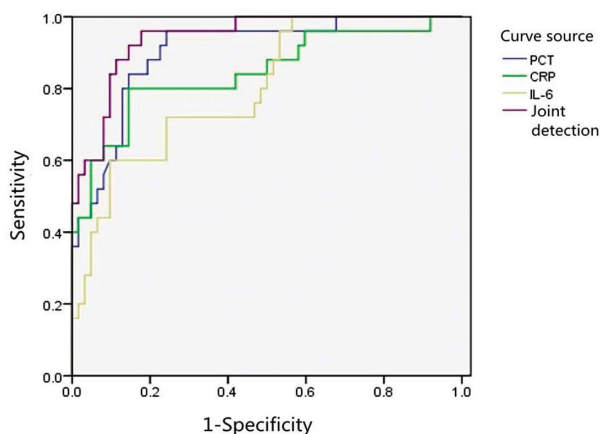


图 1 SAP 肠屏障损伤的诊断 ROC 曲线

Fig. 1 diagnostic ROC curve of SAP intestinal barrier injury

吞噬而起调理作用,从而清除病原微生物和损伤、坏死、凋亡的组织细胞^[18-20]。因此,本研究分析了 IL-6、PCT、CRP 三者与 SAP 预后及肠道屏障损伤的相关性,为临床提供一定参考。

本研究结果表明,存活组与死亡组患者胰腺坏死、APACHE II 评分、发生器官衰竭情况与 IL-6、PCT、CRP 表达水平对比差异显著($P<0.05$),与李小锋等^[21]研究相似。李小锋等研究发现,IL-6、PCT、CRP 表达水平不仅与急性胰腺炎疾病严重程度相关,而且死亡与存活患者诊断初期 IL-6、PCT、CRP 表达水平也较高。这是因为,在正常生理状态下,IL-6、PCT、CRP 等细胞因子在体内处于低表达状态,一旦受到外界刺激,会使促炎因子在机体迅速增加,刺激局部炎症反应。另外,也会使一些抗炎因子减少,导致机体内稳态失衡,引发呼吸窘迫综合征等,造成机体器官损伤^[22]。对于轻症 SAP 患者来说,全身性和局部炎症反应会对机体起到保护作用,但是若 SAP 呈现重症状态,促炎因子大量释放会对机体造成严重损害,危害患者生命安全;PCT、CRP、APACHE II 评分为重症胰腺炎患者的预后不良影响因素($P<0.05$),与李婷婷等^[23]研究相符。李婷婷等研究发现,采用促炎因子表达水平可预测患者预后情况。这是因为,IL-6 参与机体急性期反应,也就是炎性机体或组织损伤的全身性反应,随后白细胞水平增多,机体出现血管通透性增高、发热以及急性期蛋白水平增加现象^[24]。当前 PCT 作为炎症指标的一种,已经证实严重创伤、脓毒症以及感染等引起全身炎症反应的综合征情况下会增加分泌,并且血液中的浓度快速增高,从而提示疾病的严重程度与预后情况^[25]。CRP 作为炎症因子的一种,在患者发病后 6-8 h 迅速升高,72 h 能够达到峰值,属于 SAP 并未的重要标志物^[26];肠道屏障损伤组患者 IL-6、PCT、CRP 表达水平明显高于非肠道屏障损伤组 ($P<0.05$);Spear-

man 相关分析结果显示:IL-6、PCT、CRP 与肠道屏障损伤呈正相关($P<0.05$)。与 Huang Z 等研究相符。Huang Z 等^[27]研究发现,70%以上的 SAP 患者病死的主要原因为肠道屏障损伤,促使肠道内菌群紊乱,导致大量细菌、毒素等有害物质进入到血液之中,引发气管功能衰竭与感染现象,促使全身性炎症反应。另外,Yang W 等^[28]研究也发现,SAP 肠道屏障损伤患者机体 IL-6、PCT、CRP 水平较高;ROC 曲线分析显示:AUC 从低到高依次为 IL-6 (0.631)、CRP (0.667)、PCT (0.671)、联合诊断 (0.852)。血清 IL-6、PCT、CRP 的联合诊断的灵敏度与特异度明显高于血清 IL-6、PCT、CRP 单一诊断 ($P<0.05$),与 Chen Y J 等^[29]研究相似,Chen Y J 等研究发现,血清 IL-6、PCT、CRP 对 SAP 预后的联合预测高于单一诊断,而 SAP 的发生发展与肠道屏障损伤密切相关。另外,有研究发现^[30],肠道屏障损伤也参与了 SAP 发生与发展过程。因此,临床上针对 SAP 患者的预后和肠道屏障损伤可采取 IL-6、PCT、CRP 联合诊断来进行预测。

综上所述,IL-6、PCT、CRP 相关炎症因子表达水平可预测 SAP 患者预后情况,IL-6、PCT、CRP 与 SAP 肠道屏障损伤呈正相关,且三者联合对 SAP 肠道屏障损伤的诊断具有重要价值。

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