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急性胰腺炎患者血清 PAB、HMGB1、SIL-2R、ACE2 水平变化及意义 *

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摘要 目的:探讨急性胰腺炎患者血清前白蛋白(PAB)、高迁移率族蛋白B1(HMGB1)、可溶性白介素2受体(SIL-2R)、紧张素转化酶2(ACE2)水平变化及意义。**方法:**选择2018年7月至2020年7月于我院进行治疗的急性胰腺炎患者83例患者进行研究,设为病例组,并选择我院同期体检健康者70例作为对照组,分析患者血清PAB、HMGB1、SIL-2R、ACE2及急性生理功能和慢性健康状况评分系统II(APACHEII)评分水平变化情况及之间的相关性,采用受试者工作特征曲线分析血清PAB、HMGB1、SIL-2R、ACE2的诊断价值。**结果:**病例组患者血清PAB、ACE2水平显著低于对照组, HMGB1、SIL-2R、APACHEII评分水平显著高于对照组,差异显著($P<0.05$);轻症组血清PAB、ACE2水平显著高于重症组, HMGB1、SIL-2R、APACHEII评分水平显著低于重症组,差异显著($P<0.05$);Pearson相关分析结果显示,血清PAB、ACE2与APACHE II之间呈负相关($P<0.05$),血清HMGB1、SIL-2R与APACHE II之间呈正相关($P<0.05$);血清PAB预测急性胰腺炎的临界值为147.09 mg/L,灵敏度为80.54%,特异度为85.68%,AUC为0.845,血清HMGB1预测急性胰腺炎的临界值为85.34 ng/L,灵敏度为81.65%,特异度为86.69%,AUC为0.998,血清SIL-2R预测急性胰腺炎的临界值为25.47 pg/mL,灵敏度为81.59%,特异度为87.57%,AUC为0.978,血清ACE2预测急性胰腺炎的临界值为298.57 pg/mL,灵敏度为80.19%,特异度为83.58%,AUC为0.867。**结论:**血清PAB、HMGB1、SIL-2R、ACE2的表达与APACHEII评分之间密切相关,对急性胰腺炎具有较高的预测价值。

关键词:急性胰腺炎;前白蛋白;高迁移率族蛋白B1;可溶性白介素2受体;紧张素转化酶2

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Analysis of the Changes and Significance of Serum PAB, HMGB1, SIL-2R, ACE2 Levels in Patients with Acute Pancreatitis*

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ABSTRACT Objective: To study Analysis of the Changes and significance of serum Proalbumin (PAB), high mobility group protein B1 (HMGB1), soluble interleukin-2 receptor (sIL-2R), tensin converting enzyme 2 (ACE2) levels in patients with acute pancreatitis.
Methods: 83 patients with acute pancreatitis who were treated in our hospital from July 2018 to July 2020 were selected as the case group, and 70 healthy people in our hospital during the same period were selected as the control group. The changes of serum PAB, HMGB1, sIL-2R, ACE2 and acute physiology and chronic health scoring system II (APACHE II) score levels and their correlation were analyzed. The diagnostic value of serum PAB, HMGB1, sIL-2R and ACE2 was analyzed by receiver operating characteristic curve.
Results: Serum PAB and ACE2 levels in case group were significantly lower than control group, and HMGB1, sIL-2R and ApacheII scores were significantly higher than control group, the differences were significant ($P < 0.05$). Serum PAB and ACE2 levels in mild disease group were significantly higher than those in severe disease group, and the levels of HMGB1, sIL-2R and ApacheII scores were significantly lower than those in severe disease group, with significant differences ($P < 0.05$). Pearson correlation analysis, according to the results of serum PAB, ACE2 with APACHE II between negatively correlated ($P < 0.05$), serum HMGB1, SIL - 2 r and APACHE II between positively correlated ($P < 0.05$); Serum PAB predict the critical value of acute pancreatitis is 147.09 mg/L, the sensitivity was 80.54%, 85.68%, AUC is 0.845, serum HMGB1 predict the critical value of 85.34 ng/L of acute pancreatitis, the sensitivity was 81.65%, 86.69%, AUC is 0.998, serum SIL - 2 r to predict the critical value of acute pancreatitis is 25.47 pg/mL, the sensitivity was 81.59%, 87.57%, AUC is 0.978, The cut-off value of serum ACE2 for predicting acute pancreatitis was 298.57 pg/mL, the sensitivity was 80.19%, the specificity was 83.58%, and the AUC was 0.867. **Conclusion:** The expression of PAB, HMGB1, sIL-2R and ACE2 in serum was closely correlated with ApacheII score, which had a high predictive value for acute pancreatitis.

Key words: Acute pancreatitis; Prealbumin; High mobility group protein B1; Soluble interleukin-2 receptor; Tensin converting

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前言

急性胰腺炎是多种病因导致的急腹症，临床主要表现为恶心、上腹痛等症状，多是由于胰酶异常激活，诱发胰腺水肿或者坏死现象导致的，多是患者属于轻症急性胰腺炎，经有效治疗后可康复，但部分重症患者伴有脏器功能衰竭，病情凶险，死亡率较高^[1,2]。有研究显示，急性胰腺炎发病后释放各种炎症介质，增强肠黏膜通透性增，导致肠黏膜屏障功能损伤，加重胰腺的改变，增加不良预后发生率^[3]。寻找与急性胰腺炎相关的血清标志物，对疾病的早期预测具有重要意义。血清 PAB 是一种反映机体蛋白质更新过程的指标，能有效清除炎症所产生的毒性代谢物，能评估胰腺炎病情严重程度；HMGB1 可作为一种晚期炎症介质，在急性胰腺炎的发病过程中起重要作用；SIL-2R 可与 IL-2 结合，出现免疫抑制反应，目前已有研究证实其水平变化与炎症性疾病密切相关；ACE2 为肾素 - 血管紧张素系统负性拮抗因子，具有抗炎的作用，当发生胰腺炎时其水平降低^[4-7]。但目前关于 SIL-2R 与急性胰腺炎关系的相关报道较少，因此，本研究通过观察血清 PAB、HMGB1、SIL-2R、ACE2 在急性胰腺炎中的水平变化，并分析其在疾病中的意义。

1 资料与方法

1.1 一般资料

选择 2018 年 7 月至 2020 年 7 月于我院进行治疗的急性胰腺炎患者 83 例患者进行研究，设为病例组，其中男 52 例，女 31 例，年龄 33-72 岁，平均(50.14±4.14)岁，其中胆源性胰腺炎 36 例，特发性胰腺炎 24 例，酒精性胰腺炎 16 例，高脂血症性胰腺炎 7 例，根据《急性胰腺炎诊治指南 2014》^[8]将没有器官功能衰竭及局部全身并发症患者分为轻症组(n=46)，将 48 小时

内器官功能障碍患者分为重症组(n=37)；选择同期在我院进行检查的 70 例人群为对照组，其中男性 32 例，女性 38 例；年龄 32-71 岁，平均(50.02±4.31)岁。两组年龄比较差异无统计学意义($P>0.05$)。

参照《急性胰腺炎中西医结合诊疗共识意见》^[9]：伴有特征性腹痛；急性胰腺炎特征性的 CT 表现。

纳入标准：① 符合上述诊断标准；② 临床资料完整；③ 无长期服用影响检测结果的药物；④ 签署知情同意书；⑤ 非胰腺炎肿瘤患者。排除标准：① 先天免疫性疾病者；② 神志不清者；③ 合并恶性肿瘤者；④ 1 个月内有感染病史或入院前合并感染者；⑤ 无法配合相关检查者；⑥ 依从性较差者；⑦ 神志不清者；⑧ 严重肝肾疾病者。

1.2 方法

所有患者入院后开始禁食禁水，并采集 6 mL 静脉血，血清 PAB、HMGB1、SIL-2R、ACE2 采用酶联免疫吸附测定，仪器为英国 LInfinite M200 系列酶联免疫检测仪。

1.3 统计学分析

以 spss19.0 软件包处理，计量资料用均数±标准差($\bar{x} \pm s$)表示，t 检验，相关性分析使用 Spearman 相关系数，使用受试者工作特征曲线(ROC)分析血清 PAB、HMGB1、SIL-2R、ACE2 的诊断效能， $P<0.05$ 表示差异具有统计学意义。

2 结果

2.1 病例组和健康对照组血清 PAB、HMGB1、SIL-2R、ACE2 水平及 APACHEII 评分检查结果对比

病例组患者血清 PAB、ACE2 水平显著低于对照组，HMGB1、SIL-2R、APACHEII 评分水平显著高于对照组，差异显著($P<0.05$)，见表 1。

表 1 病例组和健康对照组血清 PAB、HMGB1、SIL-2R、ACE2 水平及 APACHEII 评分检查结果对比($\bar{x} \pm s$)

Table 1 Comparison of serum PAB, HMGB1, SIL-2R, ACE2 levels and ApacheII scores between the case group and healthy control group($\bar{x} \pm s$)

Groups	n	PAB(mg/L)	HMGB1(ng/L)	SIL-2R(pg/mL)	ACE2(pg/mL)	APACHEII score (points)
Case group	83	106.64±43.54	95.78±2.69	45.14±9.68	224.64±65.25	10.36±3.18
Control group	70	184.52±52.21	70.15±5.68	15.24±4.71	369.83±108.24	2.13±0.87
t value		10.062	36.551	23.587	10.219	20.991
P value		0.000	0.000	0.000	0.000	0.000

2.2 不同疾病严重程度血清 PAB、HMGB1、SIL-2R、ACE2 水平及 APACHEII 评分检查结果对比

轻症组血清 PAB、ACE2 水平显著高于重症组，HMGB1、SIL-2R、APACHEII 评分水平显著低于重症组，差异显著($P<0.05$)，见表 2。

2.3 血清 PAB、HMGB1、SIL-2R、ACE2 与急性胰腺炎 APACHEII 评分的相关性分析

经 Pearson 相关分析得知，血清 PAB、ACE2 与 APACHE

II 之间呈负相关($P<0.05$)，血清 HMGB1、SIL-2R 与 APACHE II 之间呈正相关($P<0.05$)。详见表 3。

2.4 血清 PAB、HMGB1、SIL-2R、ACE2 预测急性胰腺炎的预测价值

血清 PAB 预测急性胰腺炎的临界值为 147.09 mg/L，灵敏度为 80.54%，特异度为 85.68%，AUC 为 0.845，血清 HMGB1 预测急性胰腺炎的临界值为 85.34 ng/L，灵敏度为 81.65%，特异度为 86.69%，AUC 为 0.998，血清 SIL-2R 预测急性胰腺炎

的临界值为 25.47 pg/mL, 灵敏度为 81.59%, 特异度为 87.57%, AUC 为 0.978, 血清 ACE2 预测急性胰腺炎的临界值为 298.57

pg/mL, 灵敏度为 80.19%, 特异度为 83.58%, AUC 为 0.867, 见图 1、表 4。

表 2 不同疾病严重程度血清 PAB、HMGB1、SIL-2R、ACE2 水平及 APACHEII 评分检查结果对比($\bar{x} \pm s$)

Table 2 Comparison of serum PAB, HMGB1, sIL-2R, ACE2 levels and ApacheII score results of different disease severity($\bar{x} \pm s$)

Groups	n	PAB(mg/L)	HMGB1(ng/L)	SIL-2R(pg/mL)	ACE2(pg/mL)	APACHEII score (points)
Mild group	46	131.25±44.58	86.59±3.16	35.58±9.69	268.54±66.31	8.51±4.21
Severe group	37	76.04±27.13	107.21±4.58	57.03±10.15	170.06±52.18	12.66±3.89
T value		96.043	32.799	13.348	10.069	6.288
P value		0.000	0.000	0.000	0.000	0.000

表 3 血清 PAB、HMGB1、SIL-2R、ACE2 与急性胰腺炎 APACHEII 评分的相关性分析

Table 3 Correlation analysis of serum PAB, HMGB1, sIL-2R, ACE2 and ApacheII scores in acute pancreatitis

Indicators	APACHEII score	
	rvalue	P value
PAB	-0.528	0.000
HMGB1	0.840	0.000
SIL-2R	0.769	
ACE2	-0.503	0.000

表 4 血清 PAB、HMGB1、SIL-2R、ACE2 预测急性胰腺炎的预测价值

Table 4 The predictive value of serum PAB, HMGB1, sIL-2R and ACE2 in predicting acute pancreatitis

Indicators	Cutoff value	AUC(95%CI)	P	The sensitivity(%)	Specific degrees(%)
PAB	147.09 mg/L	0.845(0.785~0.904)	0.000	80.54	85.68
HMGB1	85.34 ng/L	0.998(0.996~1.000)	0.000	81.65	86.69
SIL-2R	25.47 pg/mL	0.978(0.955~1.000)	0.011	81.59	87.57
ACE2	298.57 pg/mL	0.867(0.807~0.928)	0.000	80.19	83.58

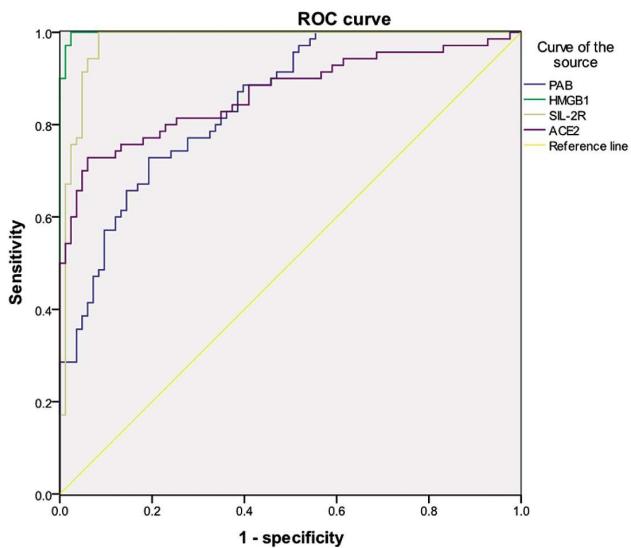


图 1 血清 PAB、HMGB1、SIL-2R、ACE2 预测急性胰腺炎的 ROC 曲线

Fig. 1 ROC curve of serum PAB, HMGB1, sIL-2R and ACE2 predicting acute pancreatitis

急性胰腺炎是常见的急腹症之一, 其中约 80% 为轻症, 并发症少, 死亡率低, 但约 20% 患者起病急, 病情严重, 还伴有胆器管功能障碍, 病死率高^[10,11]。相关研究显示, 重症急性胰腺炎死亡率高达 35%~50%, 其中发病 2 周内死亡占所有死亡患者的 60%^[12]。其发病机制尚不明确, 可能与过多饮酒、胆管内的胆结石等有关, 国外研究显示, 60% 的重症急性胰腺炎以胆源性为主^[13]。因此对急性胰腺炎进行早期预测, 并给以及时治疗预防其进展为重症, 对改善预后具有重要意义。

APACHE II 评分在极危重症患者中应用广泛, 分数越高, 病死率越高, 本研究中, 急性胰腺炎患者 APACHEII 评分水平显著高于健康人, 且病情越重分数越高。PAB 属急性负时相反应蛋白, 由肝脏所合成并在血液中分泌的, 在蛋白摄入较低的情况下, 机体内的血清前白蛋白会迅速降低^[14,15]。有研究显示, 当机体发生感染时, PAB 急剧降低, 当感染得到缓解后, 随之升高^[16]。本研究结果显示, 急性胰腺炎患者 PAB 水平显著低于健康人, 轻症组血清 ACE2 水平显著高于重症组, 且与 APACHE II 之间呈负相关, 提示, ACE2 在急性胰腺炎中表达较低, 且随着疾病的严重程度而降低, 可作为预测疾病的标志物。分析其原因可能是因为当出现急性胰腺炎时, 胰腺组织被破坏, 从而

3 讨论

引起全身性炎症反应,导致PAB下降,尤其疾病加重时下降幅度更大。HMGB1是存在于哺乳动物细胞核内的非组蛋白,具有稳定DNA结构、调节DNA转录等作用,同时也是重要的炎症介质,能促炎因子直接促进炎症发展,当机体出现炎症时, HMGB1由损伤细胞被动释放的炎症细胞主动分泌到胞外,导致其水平显著升高,从而诱发多器官功能障碍综合征等^[17-19]。有研究显示,急性胰腺炎起始于腺泡细胞受损所致的炎症反应, HMGB1作为晚期促炎因子,能诱导其他促炎因子的发展,促进急性胰腺炎的发展^[20,21]。本研究结果显示,急性胰腺炎患者 HMGB1 水平显著高于健康人,轻症组血清 HMGB1 水平显著低于重症组,且与 APACHE II 之间呈正相关,提示, HMGB1 在急性胰腺炎中呈高表达,且随着 APACHE II 的升高而升高,可作为诊断疾病的标志物水平。

SIL-2R 是 T 细胞膜活化的产物,属重要免疫抑制介质,可影响活化淋巴细胞的活性,能与 L-2 结合,抑制内分泌效应,导致免疫反应过度^[22-26]。Sholeh^[27]等研究显示,SIL-2R 在重症急性胰腺炎中表达较高,且经治疗后明显降低。本研究结果显示,急性胰腺炎患者 SIL-2R 水平显著高于健康人,轻症组血清 SIL-2R 水平显著低于重症组,且与 APACHE II 之间呈正相关,进一步提示 SIL-2R 在急性胰腺炎中表达较高,且随着疾病的严重程度而升高,可作为预测疾病的标志物。分析其原因可能是因为急性胰腺炎早期机体处于过度炎症状态,可导致 SIL-2R 上调,刺激单核细胞等释放大量炎性细胞,引起炎症损伤,由胰腺局部扩散至全身各脏器官,从而加重急性胰腺炎的严重程度。有研究显示,循环肾素-血管紧张素系统 (renin-angiotensin system, RAS) 存在于胰腺组织中,能调节胰腺导管细胞和腺泡的分泌^[28,29]。RAS 具有调节血压、维持水、电介质平衡的作用,RAS 的激活与急性胰腺炎的发生关系密切^[30]。ACE2 是血管紧张素转化酶(ACE)的同源物,一种内在膜羧肽酶,同时也是 ACE2-Ang(1-7)-Mas 新轴中的关键酶,具有抑制新血管重构、抗炎及扩张血管等作用,近年来被证实实在急性胰腺炎中表达异常^[31-34]。本研究结果显示,急性胰腺炎患者 ACE2 水平显著低于健康人,轻症组血清 ACE2 水平显著高于重症组,且与 APACHE II 之间呈负相关,提示,ACE2 在急性胰腺炎中表达较低,可作为预测疾病的标志物。Ruzzenente A^[35]等研究也显示,ACE2 升高是由于胰腺炎患者为防御胰腺病变产生的保护性反应。分析其原因可能是因为当胰腺发生炎症时,ACE2-Ang(1-7)-Mas 新轴表示上调,同时 ACE2 表达较低,引起胰腺微血管痉挛,导致胰腺微循环障碍,引起细胞坏死或凋亡,造成胰外脏器的功能障碍甚至衰竭,最终导致胰腺病变恶化。本研究进一步 ROC 分析显示,血清 PAB 预测急性胰腺炎的临界值为 147.09 mg/L, 灵敏度和特异度分别为 80.54%、85.68%; 血清 HMGB1 预测急性胰腺炎的临界值为 85.34 ng/L, 灵敏度和特异度分别为 81.65%、86.69%; 血清 SIL-2R 预测急性胰腺炎的临界值为 25.47 pg/mL, 灵敏度和特异度分别为 81.59%、87.57%; 血清 ACE2 预测急性胰腺炎的临界值为 298.57 pg/mL, 灵敏度和特异度分别为 80.19%、83.58%, 说明了血清 PAB、HMGB1、SIL-2R、ACE2 在预测急性胰腺炎时具有较高的灵敏度。

综上所述,血清 PAB、HMGB1、SIL-2R、ACE2 的表达与 APACHEII 评分之间密切相关,对急性胰腺炎具有较高的预测价值。

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