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重症高脂血症性急性胰腺炎的危险因素

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[摘要] 目的: 探讨重症高脂血症性急性胰腺炎(hyperlipidemic acute pancreatitis, HLAP)的危险因素。方法: 回顾性分析2017年6月至2020年12月间武汉大学人民医院普外科收治的162例HLAP患者的临床资料, 根据严重程度分为轻症与中度重症组($n=89$)、重症组($n=73$)。比较两组一般资料及入院第1天的实验室指标, 将两组间存在统计学差异的实验室指标全部纳入多因素二元logistic回归分析, 探究重症HLAP的独立危险因素。采用受试者工作特征(receiver operating characteristic, ROC)曲线判断各评价指标的预测性能。结果: 重症HLAP组患者心率与呼吸频率高于轻症与中度重症HLAP组, 既往有胰腺炎发作史的患者占比低于轻症与中度重症HLAP组患者, 差异均有统计学意义(均 $P<0.05$)。重症HLAP组患者中性粒细胞与淋巴细胞比值(neutrophil to lymphocyte ratio, NLR)、三酰甘油、凝血酶原时间、纤维蛋白原含量、乳酸脱氢酶水平均显著高于轻症与中度重症HLAP组患者; 预后营养指数、白蛋白、 Ca^{2+} 水平均显著低于轻症与中度重症HLAP组患者, 差异均有统计学意义。多因素二元logistic回归分析显示钙离子($OR=0.068$, $95\%CI: 0.007\sim 0.690$, $P=0.023$)水平为重症HLAP的独立保护因素, 三酰甘油($OR=1.112$, $95\%CI: 1.007\sim 1.228$, $P=0.035$)、NLR($OR=1.183$, $95\%CI: 1.011\sim 1.385$, $P=0.036$)及乳酸脱氢酶($OR=1.006$, $95\%CI: 1.000\sim 1.011$, $P=0.039$)水平为重症HLAP的独立危险因素。ROC曲线结果表明: NLR、三酰甘油、乳酸脱氢酶、 Ca^{2+} 水平及4者联合预测重症HLAP的曲线下面积(area under curve, AUC)分别为0.732、0.707、0.718、0.702、0.844, 皆具有良好的预测价值。结论: 入院第1天NLR、三酰甘油、乳酸脱氢酶、 Ca^{2+} 水平为重症HLAP的独立预测指标, 临床中应格外重视。

[关键词] 急性胰腺炎; 高脂血症; 危险因素; 预后

Risk factors for severe hyperlipidemic acute pancreatitis

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Abstract **Objective:** Hyperlipidemic acute pancreatitis (HLAP) is prone to severe, and its incidence has been increasing in recent years. This study aims to explore the risk factors of severe HLAP. **Methods:** The clinical data of 162 HLAP cases admitted to Department of General Surgery, Renmin Hospital of Wuhan University from June

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2017 to December 2020 were retrospectively analyzed. According to the severity, patients were divided into a mild or moderately severe group ($n=89$), a severe group ($n=73$). Clinical data and laboratory indicators at the first day of admission were compared between the two groups, and laboratory indicators with statistically significant differences were analyzed by binary logistic regression to explore independent risk factors for severe HLAP. Receiver operating characteristic (ROC) curve was used to determine the predictive performance of each evaluation index. **Results:** Severe HLAP patients' heart beat and respiratory rate were higher than moderately severe or mild HLAP cases, and the percentage of patients with a history of pancreatitis was lower than mild or moderately severe HLAP, with statistically significant differences. The neutrophil-lymphocyte ratio (NLR), triglyceride, prothrombin time, fibrinogen, lactate dehydrogenase levels of the severe groups were significantly higher than those in the mild or moderately severe group. The prognostic nutritional index (PNI), albumin and calcium were significantly lower than those in the mild or moderately severe group, and all the differences were statistically significant. The analysis of binary Logistic regression model showed that calcium (OR=0.068, 95%CI: 0.007-0.690, $P=0.023$) was an independent protective factor for severe HLAP, and triglyceride (OR=1.112, 95%CI: 1.007-1.228 $P=0.035$), NLR (OR=1.183, 95%CI: 1.011-1.385, $P=0.036$) and LDH (OR=1.006, 95%CI: 1.000-1.011, $P=0.039$) were independent risk factors for severe HLAP. ROC curve showed that the area under the curve (AUC) of NLR, triglyceride, lactate dehydrogenase, calcium and their combined prediction of severe HLAP were 0.732, 0.707, 0.718, 0.702, and 0.844, all of which had good predictive value. **Conclusion:** NLR, triglyceride, lactate dehydrogenase levels on the first day were independent predictors of severe HLAP, which should be paid special attention in clinical practice.

Keywords acute pancreatitis; hyperlipemia; risk factors; prognosis

急性胰腺炎(acute pancreatitis, AP)是普外科常见的危重疾病, 其中约20%为重症急性胰腺炎(severe acute pancreatitis, SAP), 病死率高达15%~20%^[1]。近年来, AP发病人数呈逐年增多趋势, 且病因谱发生明显变化, 高脂血症已跃居为我国急性胰腺炎病因的第2位^[2], 而且较其他类型的胰腺炎相比, 高脂血症性急性胰腺炎(hyperlipidemic acute pancreatitis, HLAP)发病年龄更年轻, 更易并发多器官功能障碍综合征(multiple organ dysfunction syndrome, MODS), 发展为SAP^[3]。因此, 若能明确影响HLAP预后的评分系统, 将有助于在入院后及早制订个体化的治疗方案, 从而改善HLAP的预后。目前各评分系统对于重症HLAP的预测并不一致, 且存在操作繁琐, 所需时间较长等不足^[4]。本研究探讨重症HLAP入院早期的危险因素, 旨在更简便、更准确以及更早期的评估HLAP严重程度。

1 对象与方法

1.1 对象

收集2017年8月至2020年12月首诊于武汉大学人民医院普外科的所有HLAP患者的临床资

料。纳入标准: AP诊断与分类均依据最新修订的《中国急性胰腺炎诊治指南(2021)》^[5]。HLAP的诊断标准: 1)满足AP的诊断标准; 2)入院时血清三酰甘油 ≥ 11.3 mmol/L, 或血清三酰甘油5.65~11.3 mmol/L但血清呈乳糜状; 3)排除其他病因。排除标准: 1)病例资料不全者; 2)既往严重肝肾疾病、免疫系统疾病、恶性肿瘤、营养不良的患者; 3)妊娠期胰腺炎患者; 4)起病时间超过24 h者。

1.2 治疗方式

基于《中国急性胰腺炎诊治指南(2021)》, 给予标准化、个体化、多学科协作的治疗方案, 包括禁食水、胃肠减压、液体复苏、镇痛、抑酶、降脂、营养支持、脏器功能保护与积极处理相关并发症等治疗。

1.3 观察指标

收集患者入院时的一般情况及既往史, 包括性别、年龄、体温、血压、心率、呼吸频率、糖尿病史、高血压病史、胰腺炎发作情况。入院12 h内抽取静脉血检测血常规、血生化、血脂、凝血功能等实验室指标。计算预后营养指数(prognostic nutritional index, PNI)、中性粒细胞与淋巴细胞比

值(neutrophil to lymphocyte ratio, NLR), PNI=血清白蛋白浓度+5×淋巴细胞计数($\times 10^9$)。

1.4 统计学处理

应用SPSS 23.0软件进行数据分析。计数资料以例表示, 采用 χ^2 检验或Fisher精确检验; 符合正态分布的计量资料以均数 \pm 标准差($\bar{x}\pm s$)表示, 进行样本均数独立 t 检验, 将具有统计学差异的实验室指标全部纳入多因素二元logistics回归分析, 确定重症HLAP的独立风险因素。应用Omnibus检验判断模型的全局检验情况; Hosmer-Lemeshow(H-L)检验判断模型的拟合优度。使用受试者工作特征曲线(receiver operating character, ROC)评价预测指标的诊断性能, 计算曲线下面积(area under the curve, AUC), 确定最佳的截断值, 计算预测指标

的灵敏度、特异度。 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 患者情况

共纳入162例HLAP患者, 其中轻症与中度重症89例(55%), 重症73例(45%), 男116例(72%), 女46例(28%)。年龄19~75(中位43)岁, 两组患者在性别、年龄、入院体温和血压、既往吸烟史、饮酒史、高血压病史、糖尿病史等方面差异均无统计学意义(均 $P>0.05$), 但重症HLAP患者心率($P<0.001$)、呼吸频率($P=0.005$)均明显高于轻症与中度重症HLAP患者, 轻症与中度重症HLAP患者中既往有胰腺炎病史的比例明显高于重症HLAP患者($P=0.034$, 表1)。

表1 两组患者一般情况及既往史对比

Table 1 Comparison of baseline data and previous history between the 2 groups

指标	轻症与中度重症HLAP组($n=89$)	重症HLAP组($n=73$)	χ^2/t	P
性别/例			0.065	0.799
男	63	53		
女	26	20		
吸烟史/例			1.816	0.178
有	23	26		
无	66	47		
饮酒史/例			3.292	0.070
有	14	20		
无	75	53		
高血压病/例			0.603	0.437
有	13	14		
无	76	59		
AP发作史/例			4.474	0.034
有	40	21		
无	49	52		
糖尿病史/例			2.911	0.088
有	23	28		
无	66	45		
年龄/岁	39.65 \pm 10.89	41.67 \pm 11.79	-1.132	0.260
体温/ $^{\circ}\text{C}$	36.60 \pm 0.25	36.63 \pm 0.30	-0.678	0.499
心率/ min^{-1}	84.57 \pm 15.91	96.14 \pm 20.18	-3.985	0.001
呼吸频率/ min^{-1}	19.15 \pm 2.97	20.70 \pm 3.90	-2.874	0.005
动脉压/mmHg	98.13 \pm 10.09	96.52 \pm 13.39	0.874	0.383
脉压差/mmHg	50.09 \pm 12.39	50.55 \pm 18.30	-0.189	0.850

1 mmHg=0.133 kPa.

2.2 实验室指标结果

重症HLAP组患者NLR、三酰甘油(triglyceride, TG)、凝血酶原时间(prothrombin time, PT)、纤维蛋白原含量(fibrinogen, Fib)、乳酸脱氢酶(lactate dehydrogenase, LDH)水平高于轻症与中度重症组, PNI、白蛋白(albumin, Alb)、Ca²⁺水平低于轻症与中度重症患者, 差异均有统计学意义(均 $P < 0.05$)。两组患者间血尿素氮(blood urea nitrogen, BUN)、肌酐(creatinine, Cr)、红细胞比容(hematocrit, HCT)及天门冬氨酸转氨酶(aspartate transaminase, AST)差异均无统计学意义(均 $P > 0.05$, 表2)。

2.3 重症HLAP的危险因素

将存在统计学差异的实验室指标全部纳入多因素二元logistic回归模型, 重症HLAP赋值为1, 轻

症及中度重症HLAP赋值为0, 结果提示入院第1天的Ca²⁺水平为重症HLAP的独立保护因素, TG、NLR、LDH水平为重症HLAP的独立危险因素。Omnibus检验判断模型整体具有意义($P < 0.001$); Hosmer-Lemeshow(H-L)检验判断模型的拟合优度($P = 0.574$), 提示模型拟合情况良好(表3)。

2.4 ROC曲线判断各指标预测重症HLAP的价值

Ca²⁺水平的AUC为0.702, 最佳截断值为6.095, 敏感度与特异度分别为0.849、0.506, 约登指数为0.350; TG分别为0.707、11.195、0.726、0.726、0.452; 乳酸脱氢酶分别为0.718、289.105、0.767、0.719、0.486; NLR分别为0.732、6.095、0.849、0.506、0.355。四项指标联合预测时AUC为0.844, 敏感度与特异度分别为0.753与0.775, 约登指数为0.528(表4, 图1)。

表2 两组患者实验室指标比较

Table 2 Comparison of laboratory indicators between the 2 groups

指标	轻症中度重症HLAP组(n=89)	重症HLAP组(n=73)	统计值	P
NLR	6.94 ± 4.23	11.44 ± 6.29	-5.227	<0.001
PNI	50.65 ± 6.86	46.54 ± 7.41	3.664	<0.001
Alb/(g·L ⁻¹)	42.30 ± 5.30	40.33 ± 6.72	2.037	0.044
TG/(mmol·L ⁻¹)	10.07 ± 5.07	13.96 ± 5.34	-4.747	<0.001
PT/s	10.75 ± 0.95	11.31 ± 1.20	-3.344	0.001
Fib/(g·L ⁻¹)	4.20 ± 1.73	5.50 ± 2.08	-4.275	<0.001
BUN/(mmol·L ⁻¹)	4.81 ± 1.64	5.08 ± 3.77	-0.561	0.576
Cr/(μmol·L ⁻¹)	59.63 ± 20.20	65.04 ± 40.80	-1.034	0.304
Ca ²⁺ /(mmol·L ⁻¹)	2.18 ± 0.18	1.98 ± 0.31	4.840	<0.001
LDH/(U·L ⁻¹)	278.38 ± 84.38	347.33 ± 120.17	-4.137	<0.001
AST/(U·L ⁻¹)	33.06 ± 35.87	32.23 ± 32.81	0.151	0.880
HCT	0.44 ± 0.73	0.43 ± 0.72	0.449	0.654

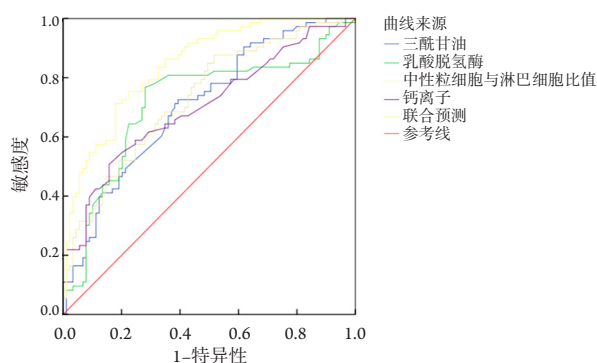
表3 重症HLAP危险因素的logistic回归分析

Table 3 Logistics analysis of risk factors for severe HLAP

指标	B	P	OR	95%CI
PNI	0.077	0.337	1.080	0.923~1.265
ALB	-0.165	0.072	0.848	0.709~1.015
TG	0.137	0.002	1.146	1.050~1.251
PT	0.045	0.850	1.046	0.655~1.672
FIB	0.219	0.109	1.245	0.652~1.629
Ca ²⁺	-2.614	0.011	0.073	0.010~0.548
LDH	0.005	0.047	1.005	1.000~1.009
NLR	0.198	0.001	1.219	1.096~1.357

表4 NLR、TG、Ca²⁺、LDH及4项指标联合预测重症HLAP的效能Table 4 Predictive value of NLR, TG, Ca²⁺, LDH and the combination of four indicators for severe HLAP

指标	AUC	95%CI	Cut-off	敏感度	特异度	约登指数	P
Ca ²⁺	0.702	0.621~0.784	2.055	0.843	0.507	0.350	0.042
TG	0.707	0.628~0.786	11.195	0.726	0.726	0.452	0.040
LDH	0.718	0.634~0.801	289.105	0.767	0.719	0.486	0.043
NLR	0.732	0.655~0.809	6.095	0.849	0.506	0.355	0.039
联合预测	0.844	0.786~0.902	—	0.753	0.775	0.528	0.030

图1 NLR、TG、Ca²⁺、LDH以及4项指标联合预测重症HLAP的ROC曲线图Figure 1 ROC curve of NLR, TG, Ca²⁺, LDH and the combination of four indicators to predict severe HLAP

3 讨论

HLAP是一种并发症多、病死率高的急腹症,近年来发病率逐年上升。如何早期识别及干预高危人群,以降低病死率一直是临床研究的焦点。HLAP的发生是一个复杂的、多因素参与的病理、生理过程,机制至今仍未完全阐明,与TG分解产生游离脂肪酸的直接损伤、胰腺微循环障碍、炎症反应、钙稳态失衡及遗传学变异等多因素相关,并非完全由TG直接作用所致^[6]。此外,AP亦可引起血脂增高,两者互为因果^[7]。迄今为止,关于TG水平与AP严重程度的确切关系尚未形成统一共识,部分学者认为两者并无关联,但愈来愈多的研究^[8-9]显示TG水平与AP严重程度呈正相关。一项纳入716例患者的前瞻性、多中心研究^[10]显示: TG水平与AP严重程度呈剂量依赖性,并且与AP患者的器官功能衰竭相关,早期降脂治疗可改善患者预后。本研究显示: TG是重症HLAP的独立危险因素,但对TG与HLAP相关并发症及预后的关联并未探讨。目前,仍需更多基础研究及前

瞻性、多中心、大样本的高质量临床研究深入揭示TG在HLAP中的作用机制,为HLAP的诊治提供理论依据。

越来越多的证据^[11]表明:表现为血清WBC、NLR、LMR等指标异常的全身炎症状态与AP严重程度密切相关,其中NLR预测性能最优。在AP初期,中性粒细胞即被活化,产生大量炎症因子与氧自由基,导致血管内皮细胞损伤、胰腺微循环障碍,同时募集并激活免疫细胞,参与全身的炎症反应,加剧胰腺局部与全身多脏器的损伤^[12]。此外,外周血淋巴细胞不仅数量减少,凋亡增多,且存在功能障碍。NLR作为一种低成本,易获得的实验室指标,综合了炎症与免疫状态的参数,其数值升高不仅可以灵敏地反映炎症状态的失衡,更是AP患者发生持续性器官功能衰竭,特别是急性肾损伤的高危因素^[13-14]。SAP合并肾损伤除与液体大量丢失和毛细血管渗漏所造成的循环容量不足及腹腔高压所导致的肾缺血相关外,还与炎症反应及其产生的毒素导致肾小管上皮细胞屏障功能受损相关^[15]。本研究表明: NLR过高是重症HLAP的独立危险因素,这与既往研究结果类似。采用ROC曲线评价其预测重症HLAP的效能, AUC值与灵敏度皆高于其他单一生化指标,表现出较优的预测价值。

LDH、Ca²⁺是临床常见的实验室指标,具有测量简便、应用广泛等优点。LDH是广泛存在于人体组织中的一种糖酵解酶,当细胞坏死时被释放入血。由此血中LDH水平可用于区分水肿性胰腺炎与坏死性胰腺炎,早期判断AP的病理类型^[16]。此外,当SAP继发器官功能衰竭等全身性并发症时,均有LDH升高, LDH升高可作为胰腺炎诊断及预后的早期评价指标,预测性能并不亚于RASON评分^[17-18]。Ca²⁺作为第二信使,在胰腺腺泡细胞内信号转导、腺泡细胞内蛋白酶原的活化中发挥重要作用^[19]。发生SAP时,一方面为保持细胞内Ca²⁺的稳

态, 会调控细胞膜及胞内各种离子通道, 使得循环系统中 Ca^{2+} 水平降低; 另一方面脂肪坏死分解后形成脂肪酸, 与血液中 Ca^{2+} 结合形成脂肪酸钙沉积在局部组织中, 进一步造成血清中 Ca^{2+} 降低^[20]。血清中 Ca^{2+} 减少易引起全身炎症反应综合征、器官功能衰竭等并发症, 加重患者病死率^[21]。临床中单个检测指标的应用往往不能满足某些疾病诊断, 有时需将几个检测项目联合应用, 目的是提高诊断效能。4项指标联合预测时虽敏感度不及NLR单一预测, 但特异度提升较大, 且AUC与约登指数明显增大, 综合预测性能相对更优, 表现出良好的临床应用价值。

由于本研究为单中心的回顾性研究, 相比于前瞻性研究存在一定选择偏倚, 入组患者有限, 不能代表整个患病人群, 存在一定局限性, 所得结论还有赖多中心大样本的临床研究进一步论证。

本研究结果表明: 入院第1天血清NLR、TG、LDH与 Ca^{2+} 水平对HLAP严重程度的评估具有一定价值, 临床中应引起重视。对此类指标异常的患者应给予针对性治疗措施, 防止病情的恶化。

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