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· 临床研究 ·

未成熟粒细胞百分率在重症急性胰腺炎早期评估中的临床价值

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摘要

背景与目的: 重症急性胰腺炎 (SAP) 是常见的急腹症, 其进展快、并发症多、病死率高, 而 SAP 的早期识别对指导临床治疗、改善患者预后有着重要意义。未成熟粒细胞百分率 (IG%) 是一种新兴的炎性指标, 在疾病早期即可出现明显变化。鉴于炎性指标在 SAP 的发生发展中起着关键作用, 本研究探讨 IG% 在 SAP 早期评估中的临床价值。

方法: 回顾性分析 2010 年 1 月—2019 年 10 月期间 521 例根据指南确诊为急性胰腺炎 (AP) 的患者临床资料, 其中 63 例为 SAP (SAP 组), 458 例轻症或中重症 AP (非 SAP 组)。比较两组患者的临床特征、IG%、白细胞 (WBC) 计数、中性粒细胞与淋巴细胞比率 (NLR)、C 反应蛋白 (CRP)、淀粉酶水平等指标, 采用受试者工作特征曲线 (ROC) 分析各炎性指标对 SAP 的诊断效能。

结果: SAP 组的病死率为 2.2% (18/63), 非 SAP 组为 28.6% (10/458); SAP 组患者较非 SAP 组患者年龄偏大、ICU 入住与行外科治疗比例高、住院时间长 (均 $P < 0.05$)。SAP 组 IG%、WBC、NLR、CRP 均明显高于非 SAP 组 (均 $P < 0.05$), 但两组血清淀粉酶水平无统计学差异 ($P = 0.163$)。ROC 曲线分析结果显示, IG%、WBC、NLR、CRP 对预测 SAP 的有效性均有统计学意义 (均 $P < 0.05$); IG% 在最佳临界值为 0.9 时的曲线下面积 (AUC) 为 0.973, 敏感度为 100%, 特异度为 93.8%, 明显优于 WBC (AUC: 0.665; 敏感度: 66.6%; 特异度: 87.6%)、NLR (AUC: 0.752; 敏感度: 73.3%; 特异度: 76.5%)、CRP (AUC: 0.802; 敏感度: 100%; 特异度: 54.9%)。

结论: 血常规中 IG% > 0.9 可能是早期胰腺坏死的重要指标, 与其他传统炎性指标相比, IG% 可能是一种更有效、更可靠的 SAP 早期预测指标。

关键词

胰腺炎, 急性坏死性 / 诊断; 炎症; 未成熟的粒细胞百分率

中图分类号: R657.5

Clinical value of immature granulocyte percentage in early evaluation of severe acute pancreatitis

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Abstract

Background and Aims: Severe acute pancreatitis (SAP) is a dangerous acute abdominal disorder, characterized by rapid progression, numerous complications and high mortality. Early detection of SAP may helpful for guiding

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the clinical treatment and improving the prognosis of the patients. Immature granulocyte percentage (IG%) is an emerging inflammatory indicator, which may display an obvious change in the early stage of diseases. Considering the inflammatory indicators play crucial roles in the development of SAP, this study was to conducted to evaluate the clinical value of IG% in the early detection of SAP.

Methods: The clinical data of 521 patients diagnosed as acute pancreatitis (AP) according to the guidelines from January 2010 to October 2019 were retrospectively analyzed. Of the patients, 63 cases were SAP (SAP group) and 458 cases were mild or moderately severe AP (non-SAP group). The clinical features and the variables that included IG%, white blood cell (WBC) count, neutrophil to lymphocyte ratio (NLR), C-reactive protein (CRP) and amylase level were compared between the two groups of patients. The diagnostic efficiency of each inflammatory indicator for SAP was determined by receiver operating characteristic curve (ROC) analysis.

Results: The mortality rate in SAP group was 2.2% (18/63) and in non-SAP group was 28.6% (10/458); the patients was older, and the proportions of cases requiring ICU admission and surgical intervention were higher and the length of hospital stay was longer in SAP group than those in non-SAP group (all $P < 0.05$). The levels of IG%, WBC, NLR and CRP in SAP group were significantly higher than those in non-SAP group (all $P < 0.005$), but there was no significant difference in serum the amylase levels between the two groups ($P = 0.163$). The results of ROC analysis showed that the diagnostic powers of IG%, WBC, NLR and CRP for SAP were all had significance (all $P < 0.005$); the area under the curve (AUC) of IG% in predicting SAP was 0.973, with a sensitivity of 100% and specificity of 93.8% at the optimal cut-off value of 0.9, which was superior to WBC (AUC: 0.665, sensitivity: 66.6%, specificity: 87.6%), NLR (AUC: 0.752, sensitivity: 73.3%, specificity: 76.5%) and CRP (AUC: 0.802, sensitivity: 100%, specificity: 54.9%).

Conclusion: The IG% value in the blood routine greater than 0.9 may be an early indicator for pancreatic necrosis. Compare to traditional inflammatory indicators, IG% is more effective and reliable predictor of SAP.

Key words

Pancreatitis, Acute Necrotizing/diag; Inflammation; Immature Granulocyte Percentage

CLC number: R657.5

急性胰腺炎 (acute pancreatitis, AP) 是一种常见的消化系统疾病, 发病率呈逐年升高趋势^[1], 依据病情严重程度一般分为轻症 (MAP)、中重症 (MSAP) 和重症急性胰腺炎 (SAP)^[1-3], 其中 SAP 在所有 AP 中发病率为 9%~20%^[4-5]。尽管近年来诊断技术和治疗水平有所提高, 但 SAP 的病死率仍高达 20%~30%^[3], 多数患者仍需在重症监护病房进行积极的支持性治疗^[6], 已成为严重危及我国人民健康和生命的重大疾病之一。入院后最初 24 h 是 SAP 诊疗的最佳窗口期, 能否及时给予恰当处置, 将直接决定病情的最终转归^[7], 在诊断和治疗中的任何时机延误都会导致病死率的增加^[8]。因此, 在疾病的起步阶段准确评估病情严重程度和疾病走势, 及早识别可能进展为 SAP 的患者, 早期采取积极有效的干预措施, 有望降低 SAP 的病死率和并发症发生率, 对改善临床预后意义重大。

目前存在较多用于评估 SAP 病情严重程度和病死率的多因素评分系统^[9-12] (主要是基于临床、影

像学证据和实验室检测) 以及单因素评价指标^[12-13] (生物学标志物), 虽然其侧重点和临床价值各不相同, 但由于各种限制 (如反应时间、患者依从性和敏感度等), 这些评分大部分不能立即使用。因此, 在发病早期需要一种快速、可靠的生物指标对患者进行评估, 这将有助于识别 SAP 患者, 进而予以临床干预, 从而改善此类患者预后。

未成熟粒细胞百分率 (immature granulocyte percentage, IG%) 是一种新的炎性指标^[14-17], 大多数外科医师对其认识不足。外周血中未成熟粒细胞的检测是骨髓增生和严重感染的一个指标, 而健康人群中通常不存在这种情况^[14-16]。由于自动化血液学分析仪的技术进步, IG% 可以通过常规全血细胞计数轻松、快速地测定^[16]。最近的研究^[17-20]表明, 在预测感染严重程度方面, IG% 比传统的指标如白细胞 (WBC) 计数、C-反应蛋白 (CRP) 和中性粒细胞淋巴细胞比值 (NLR) 更有效。本研究的目的是明确 IG% 作为炎性指标在 SAP

早期预测中的作用。

1 资料与方法

1.1 一般资料

本研究回顾性收集盘锦市中心医院普通外科2010年1月—2019年10月期间因AP入院治疗的521例患者临床资料,其中男345例,女176例。全部患者或患者家属知晓诊疗方案并签署治疗同意书。

患者入院后在未接受任何治疗方式前抽取静脉血,检测血常规、肝肾功、CRP、血淀粉酶等指标,以获取WBC计数、中性粒细胞计数、淋巴细胞计数和IG%、CRP、淀粉酶。

1.2 纳入排除标准和分组

符合AP诊断标准^[1-3]纳入本研究,排除标准:(1)伴有血液系统疾病或近1周内合并感染性疾病者;(2)入院72 h内没有完成腹部增强CT的患者;(3)转往其他医院或自行出院的患者。本研究仅纳入期间多次入院的患者的首次就诊数据,而不考虑就诊次数。根据《中国急性胰腺炎诊治指南(2019,沈阳)》将患者分为非SAP组(MAP和MSAP)和SAP组。分析全部患者临床特征及炎症指标(WBC、IG%、NLR、CRP),并进行两组比较。

1.3 统计学处理

应用SPSS 18.0统计软件进行分析,连续变量表示为均值±标准差($\bar{x} \pm s$),组间比较采用 χ^2 检验和Mann-Whitney U检验。进行受试者工作特征曲线(ROC)分析,以确定WBC、NLR、CRP和IG%等指标对SAP的评估价值和最佳临界值。根据获得的最佳临界值,计算阳性预测值(PPV)和阴性预测值(NPV), $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 两组患者一般资料比较

521例AP患者中,非SAP组458例(87.9%)和SAP组63例(12.1%)。全组总计28例患者死于相关并发症,其中非SAP组10例(10/458,2.2%),SAP组18例(18/63,28.6%)。

两组患者在性别上差异无统计学意义

($P=0.517$);SAP组患者的年龄明显高于非SAP组($P=0.002$);在ICU接受治疗方面,SAP组(59/63,93.7%)明显多于非SAP组(27/458,5.9%, $P < 0.001$);在外科治疗方面,SAP组患者37例(58.7%)接受了手术治疗(坏死性切除、清创、灌洗、引流),比例明显高于非SAP组(7.9%, $P < 0.001$);在病因学上,全部患者中395例(75.8%)为胆源性病变,96例(18.4%)为高脂血症^[1,3,21]所致,30例(5.8%)为酒精性病变,两组无统计学差异($P=0.279$);SAP组住院治疗时间明显长于非SAP组($P=0.001$)(表1)。

表1 两组患者临床病理特征的比较
Table 1 Comparison of clinicopathologic features between the two groups

变量	例数 (n)	非SAP组 (n=458)	SAP组 (n=63)	P
性别[n(%)]				
男	345	301(65.7)	44(69.8)	0.517
女	176	157(34.3)	19(30.2)	
年龄(岁, $\bar{x} \pm s$)	521	47.4 ± 15.5	55.1 ± 17.8	0.002
是否入ICU[n(%)]				
有	86	27(5.9)	59(93.7)	<0.001
无	435	431(94.1)	4(6.3)	
手术治疗[n(%)]				
有	73	36(7.9)	37(58.7)	<0.001
无	448	403(92.1)	26(41.3)	
病因[n(%)]				
胆源性	395	343(74.9)	52(82.5)	0.279
高脂血症	96	89(19.4)	7(11.1)	
酒精性	30	26(5.7)	4(6.3)	
住院时间(d, $\bar{x} \pm s$)	521	9.2 ± 4.8	14.4 ± 10.9	0.001

2.2 两组患者炎症指标比较

SAP组WBC、NLR、CRP、IG%平均水平明显高于非SAP组($P=0.010$ 、 $P=0.003$ 、 $P=0.002$ 、 $P < 0.001$),非SAP组与SAP组血清淀粉酶水平无统计学差异($P=0.163$)(表2)。

表2 两组炎症指标和淀粉酶的比较($\bar{x} \pm s$)
Table 2 Comparison of inflammation indicators and amylase levels between the two groups($\bar{x} \pm s$)

指标	非SAP组 (n=458)	SAP组 (n=63)	P
WBC($10^9/L$)	11.6 ± 2.8	12.7 ± 3.1	0.010
NLR	2.4 ± 0.7	2.8 ± 1.0	0.003
CRP(mg/L)	16.9 ± 8.2	21.1 ± 9.8	0.002
IG%	0.5 ± 0.1	1.4 ± 0.7	<0.001
血淀粉酶水平(U/L)	345.8 ± 107.4	323.5 ± 119.2	0.163

2.3 SAP 组患者炎症指标比较

绘制SAP组患者ROC曲线，计算SAP组患者WBC、NLR、CRP、IG%的最佳临界值（图1）。各指标预测SAP的有效性均有统计学意义（均 $P < 0.05$ ），但IG%对SAP组患者预测的强度高于其他指标（IG% AUC: 0.973，敏感度为100%，特异度为93.8%）；PPV 79.8%，NPV 100%，ROC曲线分析结果见表3。

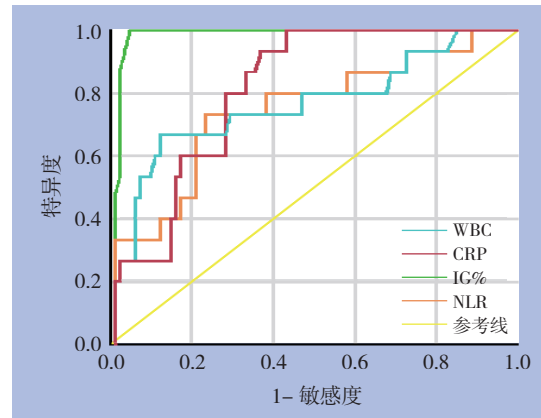


图 1 炎症指标诊断 SAP 的 ROC 曲线

Figure 1 ROC curves of the inflammatory indicators for diagnosis of SAP

表 3 炎症指标对预测 SAP 病情的 ROC 分析

Table 3 ROC analysis of inflammation indicators for prediction of SAP

指标	AUC	95% CI	临界值	敏感度	特异度	PPV	NPV	P
WBC	0.665	0.576~0.812	12.4	66.6	87.6	50.4	92.4	0.001
NLR	0.752	0.615~0.896	2.7	73.3	76.5	36.7	93.5	0.002
CRP	0.802	0.714~0.899	19	100	54.9	32.2	100	<0.001
IG%	0.973	0.955~1	0.9	100	93.8	79.8	100	<0.001

3 讨论

在本研究中SAP比例为12.1%（63/521），与既往的文献^[4-5]报道一致，而SAP患者的年龄、ICU入住率及外科手术治疗方面均明显高于非SAP组，其总住院时间和患者家庭所承担的医疗费用也是明显高于非SAP组患者。由此表明SAP是特别需要普外科、ICU及介入科等多学科、多种治疗模式支持的重症疾病，治疗过程困难重重且费用高昂，随着SAP病情的进展，多器官衰竭的发生率和病死率也随之增加^[22-24]。因此，SAP的早期预测对于降低病死率和降低医疗费用具有极为重要的临床意义^[3,24]。

针对SAP病情评估，现阶段存在各类评分系统，Ranson评分和Glasgow评分是较为经典的病情评分系统。SAP患者的病死率随Ranson评分总分的增加而升高，其判断预后不佳的灵敏度为70%~80%，但其缺陷也是非常明显的，一方面纳入指标过多，且比较繁琐，又未能将影像学的改变（如是否合并胰腺坏死）和器官衰竭对预后的重大影响纳入^[25]；另一方面需在入院48 h后进行，而SAP患者常在入院24 h内即出现多器官衰竭，故并不能早期预测病情的进展程度^[26]。Glasgow评分

与Ranson评分相似，都是基于实验室指标和人口学资料^[27]，但Glasgow评分的部分指标需在入院24 h后才可确定，故同样难以用于SAP的早期预测^[28]。急性生理与慢性健康评分II（APACHE II）是危重症领域应用最广泛的评分系统^[10,29]，在起病8 h内评分上升即可提示进展为SAP的风险增加，同时也可每日重复评分以评估疾病发展的趋势。但有研究表明，入院24 h内APACHE II在预测SAP上的NPV可达86%，而PPV仅为43%，说明该评分用于排除SAP的临床价值明显优于预测SAP^[30]。另外，由于评分计算的复杂性，临床应用受到一定限制^[31]。

血清淀粉酶是临床工作中最为常见的胰腺炎相关标记物，一般在发病4~6 h后升高，并在3~5 d内逐步恢复到正常水平。淀粉酶水平对诊断很重要，但对病情的严重程度并不能有效评估^[32]。本研究中非SAP组与SAP组血清淀粉酶水平无显著性差异（ $P=0.163$ ），表明其在SAP诊疗的最佳时间窗内并无实际临床意义^[33]。

近年来研究人员陆续发现CRP、CRP/白蛋白比值、NLR、降钙素原等炎症指标与胰腺炎病情相关^[34-39]。其中常用于的指标是CRP，一种由肝细胞合成急性期反应物，其异常升高反应急性炎

症和组织损伤时促炎细胞因子释放的过程^[40]。有研究^[34-35]报道称当CRP在最初48 h内达到1 500 mg/L的临界值时,其预测SAP的敏感度和特异度为80%,准确率为86%,但在本研究预测SAP时,CRP的临界值>19 mg/L,敏感度为100%,特异度为54.9%,说明其敏感度虽然可靠,但特异度不强。

全身炎症反应可导致循环中的白细胞成分平衡发生改变,分别介导中性粒细胞的增加和淋巴细胞数量的减少,而NLR被认为更优于WBC总数对病情的严重性的识别。因此有学者^[41]提出NLR可作为全身炎症反应的代表性指标,而不是WBC总数。另有研究^[42]认为,NLR升高表明SAP病情较重和可能伴有器官衰竭的存在,但这需要通过观察NLR持续变化才具有临床意义。在本研究中NLR的截止值>2.7,预测SAP的敏感度为73.3%,特异度为76.5%。因此,无论是NLR亦或是WBC总数仅对评估胰腺坏死的严重程度有重要意义,但在早期评估中的临床意义有限。

腹部增强CT尤其是薄层CT重建是评估SAP最有效的方法^[3, 11, 43],随着胰腺组织坏死数量的增加,器官衰竭和病死率也随之增加^[11]。这些研究还表明,通过增强CT检测到的胰腺形态学改变与患者的临床结果有很强的相关性。相关研究^[43]认为,患者自发病72 h内实施腹部增强CT对AP的诊断和胰腺坏死等并发症的评估具有重要作用。在本研究SAP组中15例患者入院24 h内行腹部CT时并不支持SAP征象,至发病48 h后复查腹部CT才得以确诊,说明在SAP发病早期增强CT的敏感度是有限的。基于此,笔者单位近年来对所有AP患者入院后48~72 h内临床症状未改善的患者均行增强CT,以便指导临床制定个体化治疗方案。

综上,SAP的早期诊断迫切需要一种理想的能够独立应用于临床的指标,这种理想的生物指标应该具有早期、快速、简单、容易测量、高度准确和经济有效等特点,而以上指标或检查均存在自身的局限性。近年来IG%已被研究人员作为一个新型和有前途的炎症指标^[15, 17],因为即便WBC总数和绝对中性粒细胞数在重症急性感染早期正常,IG%也会增加。此外,IG%也可反映重症感染病例治疗的疗效^[15]。有研究^[44]认为相较于其它炎症指标,IG%在SAP患者早期诊断中作用

更佳。本研究发现非SAP组和SAP组的所有炎症指标(WBC、NLR、CRP和IG%)均有统计学差异,当IG%>0.9时,其敏感度为100%,特异度为93.8%,PPV为79.8%,NPV为100%,表明作为SAP早期识别指标,其临床价值明显优于其它炎症指标,具有较强的临床应用意义。本研究SAP组病死率为28.6%(18/63),但需指出的是其中72.2%(13/18)的患者为早年间病例,在近年来通过对IG%的充分认识,加之多学科模式的应用^[45],使得部分患者在疾病早期即开始注重个体化治疗,其并发症发生和病死率明显下降。

本研究有几个局限性。一方面,由于SAP的患病率较低,虽然收集了近10年的资料,但SAP患者仅有63例,组间比较的选择性偏移无法避免。因此,为了评估IG%对SAP更准确的预测价值,还应进行大规模、多中心试验研究。另一方面,本研究是基于医疗记录的回顾性研究。在回顾性研究中,实验设计和统计分析并不能完全控制混杂因素,如本研究仅将伴有血液系统疾病和近期患有感染性疾病的患者排除,但无法除外潜在伴随者。

本研究结果显示,与WBC、NLR、CRP等传统炎症指标相比,IG%是一种更有效、更可靠的SAP早期预测指标,无需额外的时间和费用,且易于获得。在尚未确诊为SAP的患者中,血常规中IG%>0.9是胰腺坏死的重要早期指标,这一结果因患者血流动力学不稳定而无法完成腹部增强CT的情况下更为重要,外科医生应予以重视,应密切观察此类患者的病情变化,根据患者自身情况,制定个体化治疗方案,避免贻误治疗的最佳时机。

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