

粪便 S100A12, 钙卫蛋白和乳铁蛋白对溃疡性结肠炎患者疾病活动度和黏膜愈合评估价值分析

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摘要: 目的 分析粪便 S100A12, 钙卫蛋白 (fecal calprotectin, FC) 和乳铁蛋白 (lactoferrin, LF) 对溃疡性结肠炎 (ulcerative colitis, UC) 患者疾病活动度和黏膜愈合情况的评估价值。方法 选取 2018 年 9 月 ~ 2020 年 7 月期间营口市中心医院收治的 UC 患者 125 例, 根据疾病活动度将其分为缓解组 (72 例) 和活动组 (53 例), 缓解组再根据黏膜情况分为黏膜愈合组 (34 例) 和黏膜病变组 (38 例)。检测所有患者的粪便 S100A12, FC 和 LF 水平, 采用 Pearson 法分析粪便 S100A12, FC, LF 与 UC 镜下严重程度指数 (UCEIS 评分) 的相关性, 采用受试者操作特征曲线 (ROC) 分析粪便 S100A12, FC 和 LF 对 UC 患者疾病活动度和黏膜愈合的评估价值。结果 活动组的粪便 S100A12 ($1.21 \pm 0.36 \mu\text{g/g}$), FC ($326.38 \pm 153.54 \mu\text{g/g}$) 和 LF ($288.62 \pm 164.84 \mu\text{g/g}$) 水平均明显高于缓解组 ($0.75 \pm 0.24 \mu\text{g/g}$, $138.52 \pm 63.28 \mu\text{g/g}$, $103.25 \pm 45.63 \mu\text{g/g}$), 差异有统计学意义 ($t=8.566 \sim 9.367$, 均 $P<0.05$); 黏膜病变组的粪便 S100A12 ($0.99 \pm 0.29 \mu\text{g/g}$), FC ($188.94 \pm 70.94 \mu\text{g/g}$) 和 LF ($142.31 \pm 63.21 \mu\text{g/g}$) 水平明显高于黏膜愈合组 ($0.48 \pm 0.21 \mu\text{g/g}$, $82.17 \pm 33.61 \mu\text{g/g}$, $59.56 \pm 20.52 \mu\text{g/g}$), 差异均有统计学意义 ($t=7.295 \sim 8.458$, 均 $P<0.05$)。经 Pearson 分析显示, UC 患者的粪便 S100A12, FC, LF 水平与 UCEIS 评分均呈正相关 ($r=0.426, 0.438, 0.417$, 均 $P<0.05$); ROC 分析显示, 粪便 S100A12, FC, LF 对 UC 患者疾病活动度和黏膜愈合有一定的评估价值, 且三者联合应用可有效提升评估价值, 评估疾病活动度的曲线下面积为 0.895, 敏感度和特异度分别为 88.70% 和 90.28%, 评估黏膜愈合的曲线下面积为 0.890, 敏感度和特异度分别为 91.18% 和 86.84%。结论 粪便 S100A12, FC 和 LF 联合应用对 UC 患者疾病活动度和黏膜愈合的评估价值较高, 具有一定的临床应用价值。

关键词: 溃疡性结肠炎; S100A12; 钙卫蛋白; 乳铁蛋白

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Evaluation Value of Stool S100A12, Fecal Calprotectin and Lactoferrin for Disease Activity and Mucosal Healing in Patients with Ulcerative Colitis

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Abstract: Objective To analyze the value of stool S100A12, fecal calprotectin (FC) and lactoferrin (LF) in the evaluation of disease activity and mucosal healing in patients with ulcerative colitis (UC). **Methods** 125 patients with UC admitted to Yingkou Central Hospital from September 2018 to July 2020 were selected, and they were divided into remission group (72 cases) and active group (53 cases) according to disease activity. The remission group was further divided into mucosal healing group (34 cases) and mucosal lesion group (38 cases) according to the mucosal condition. The levels of stool S100A12, FC and LF in all patients were detected. Pearson method was used to analyze the correlation between stool S100A12, FC, LF and UC microscopic severity index (UCEIS score). Receiver operating characteristic curve (ROC) was used to analyze the evaluation value of stool S100A12, FC and LF for disease activity and mucosal healing of patients with UC. **Results** The levels of stool S100A12 ($1.21 \pm 0.36 \mu\text{g/g}$), FC ($326.38 \pm 153.54 \mu\text{g/g}$) and LF ($288.62 \pm 164.84 \mu\text{g/g}$) in the active group were significantly higher than those in the remission group ($0.75 \pm 0.24 \mu\text{g/g}$, $138.52 \pm 63.28 \mu\text{g/g}$, $103.25 \pm 45.63 \mu\text{g/g}$), the differences were statistically significant ($t=8.566 \sim 9.367$, all $P<0.05$). The levels of stool S100A12 ($0.99 \pm 0.29 \mu\text{g/g}$), FC ($188.94 \pm 70.94 \mu\text{g/g}$) and LF ($142.31 \pm 63.21 \mu\text{g/g}$) in the mucosal lesion group were significantly higher than those in the mucosal healing group ($0.48 \pm 0.21 \mu\text{g/g}$, $82.17 \pm 33.61 \mu\text{g/g}$, $59.56 \pm 20.52 \mu\text{g/g}$), and the difference were statistically significant ($t=7.295 \sim 8.458$, all $P<0.05$). Pearson analysis showed that the levels of stool S100A12, FC and LF in patients with UC were positively correlated with the UCEIS score ($r=0.426, 0.438, 0.417$, all $P<0.05$). ROC analysis showed that stool S100A12, FC and LF had certain evaluation value for disease activity and mucosal healing of patients with UC, and the combined

application of the three could effectively improve the evaluation value, the area under the curve for assessing disease activity was 0.895, the sensitivity and specificity were 88.70% and 90.28%, respectively. The area under the curve for assessing mucosal healing was 0.890, and the sensitivity and specificity were 91.18% and 86.84%, respectively. **Conclusion** Stool S100A12, FC and LF combined application of disease activity and mucosal healing in patients with UC have a high evaluation value, and it has a certain clinical application value.

Keywords: ulcerative colitis; S100A12; fecal calprotectin; lactoferrin

溃疡性结肠炎 (ulcerative colitis, UC) 是炎症性肠病的常见类型, 目前临床尚缺乏有效根治的治疗方法, 患者病情常在缓解和复发之间交替发作, 准确评估患者的病情对于临床治疗方案的确定有重要的指导作用^[1]。在过去临床主要根据疾病活动度来评估 UC 患者的病情以及治疗效果, 但近年来临床越来越重视患者的黏膜愈合情况, 相关研究显示^[2], 黏膜愈合与降低复发率、减少住院治疗以及手术治疗密切相关, 目前临床缓解和黏膜愈合已成为轻、中度患者临床治疗的主要终点^[3]。肠镜检查是评估 UC 患者病情的金标准, 但其作为一种侵入性检查会给患者带来较大的痛苦, 仅适合作为诊断手段, 不适宜频繁地实时评估患者的肠黏膜病变情况。S100A12 是近年来发现的一种 UC 生物标志物, 李慕然等^[4]人的研究发现, 血清 S100A12 的表达水平与 UC 患者的病情密切相关, 然而 S100A12 与黏膜愈合的关系尚不清楚。钙卫蛋白 (fecal calprotectin, FC) 和 乳铁蛋白 (lactoferrin, LF) 均是常见的 UC 粪便生物标志物, 可较好地反映患者的疾病活动度^[5-6], 但尚缺乏二者与 UC 患者黏膜愈合的研究。本研究旨在探讨粪便中 S100A12, FC 和 LF 对 UC 患者疾病活动度和黏膜愈合的评估价值, 以期临床采用无创方法评估患者病情提供参考, 现作如下报道。

1 材料与方法

1.1 研究对象 选取 2018 年 9 月 ~ 2020 年 7 月期间营口市中心医院收治的 UC 患者 125 例, 其中男性 72 例, 女性 53 例, 年龄 22 ~ 63(41.32 ± 10.35) 岁。纳入标准: ①均符合《炎症性肠病诊断与治疗的共识意见 (2018 年, 北京)》中关于 UC 的诊断标准^[7]; ②年龄 18 ~ 70 岁; ③患者及其家属对本次研究内容知情同意。排除标准: ①近期患有急性感染性胃肠疾病或上消化道糜烂、溃疡者; ②并发有恶性肿瘤者; ③并发有自身免疫性疾病、除 UC 以外的炎症性疾病者; ④并发有肠麻痹、巨结肠等严重并发症; ⑤妊娠或准备妊娠、哺乳期妇女。本次研究已通过我院伦理委员会的批准。

1.2 仪器与试剂 S100A12, FC 和 LF 试剂盒 (英国 Abcam 公司); 酶标仪 (美国 BIO-RAD 伯乐 680)。

1.3 方法 采用 UC 镜下严重程度指数 (UCEIS

评分) 进行分组, UCEIS 评分分别从出血情况、血管纹理、糜烂和溃疡对受累肠段进行评估, 以病变最严重部位处评分总和作为最终的 UCEIS 评分, 该评分满分为 8 分, 得分越高代表病情越严重。若 UCEIS 评分为 0 ~ 1 分, 则纳入到缓解组 (72 例); UCEIS 评分为 2 ~ 8 分, 则纳入到活动组 (53 例)。缓解组再根据黏膜情况进行分组, 若肠镜下未见明显异常 (UCEIS 评分 = 0 分), 则纳入到黏膜愈合组 (34 例), 若肠镜下可见炎症细胞浸润 (UCEIS 评分 = 1 分), 则纳入到黏膜病变组 (38 例)。患者于肠镜检查前 1 天留取晨起第 1 次粪便标本, 采用酶联免疫吸附法检测粪便中的 S100A12, FC 和 LF 水平, 严格遵循试剂盒说明书内容进行检测。

1.4 统计学分析 采用 SPSS22.0 对数据进行统计分析。计量资料经检验均符合正态分布, 以均值 ± 标准差 ($\bar{x} \pm s$) 的形式表示, 采用 *t* 检验。采用 Pearson 进行相关性分析。采用受试者操作特征曲线 (receiver operating characteristic curves, ROC) 分析粪便 S100A12, FC 和 LF 对 UC 患者疾病活动度和黏膜愈合的评估价值。 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 缓解组和活动组的粪便 S100A12, FC, LF 水平比较 活动组的粪便 S100A12 ($1.21 \pm 0.36 \mu\text{g/g}$), FC ($326.38 \pm 153.54 \mu\text{g/g}$) 和 LF ($288.62 \pm 164.84 \mu\text{g/g}$) 水平均明显高于缓解组 ($0.75 \pm 0.24 \mu\text{g/g}$, $138.52 \pm 63.28 \mu\text{g/g}$, $103.25 \pm 45.63 \mu\text{g/g}$), 差异有统计学意义 ($t = 8.566, 9.367, 8.600$, 均 $P < 0.05$)。

2.2 黏膜愈合组和黏膜病变组的粪便 S100A12, FC, LF 水平比较 黏膜病变组的粪便 S100A12 ($0.99 \pm 0.29 \mu\text{g/g}$), FC ($188.94 \pm 70.94 \mu\text{g/g}$) 和 LF ($142.31 \pm 63.21 \mu\text{g/g}$) 水平均明显高于黏膜愈合组 ($0.48 \pm 0.21 \mu\text{g/g}$, $82.17 \pm 33.61 \mu\text{g/g}$, $59.56 \pm 20.52 \mu\text{g/g}$), 差异有统计学意义 ($t = 8.458, 8.005, 7.295$, 均 $P < 0.05$)。

2.3 UC 患者的粪便 S100A12, FC 和 LF 水平与 UCEIS 评分的相关性 经 Pearson 分析显示, UC 患者的粪便 S100A12, FC 和 LF 水平与 UCEIS 评分均呈正相关 ($r = 0.426, 0.438, 0.417$, 均 $P < 0.05$)。

2.4 粪便 S100A12, FC 和 LF 对 UC 患者疾病活

活动度的评估价值 见表1, 图1。以活动组患者的数据为阳性样本, 以缓解组患者的数据为阴性样本, 采用ROC分析粪便S100A12, FC和LF对UC患者疾病活动度的评估价值。结果显示, 粪便FC, LF对UC患者疾病活动度的评估价值较高, 曲线

下面积均在0.8以上, 而S100A12的评估价值稍低, 曲线下面积为0.792。三者联合应用可进一步提高对UC患者疾病活动度的评估价值, 曲线下面积可提升至0.895, 敏感度和特异度分别为88.70%, 90.28%。

表1 粪便S100A12, FC, LF对UC患者疾病活动度的评估价值

项目	曲线下面积	95CI%	最佳截断值	敏感度(%)	特异度(%)
S100A12	0.792	0.709 ~ 0.875	1.11 $\mu\text{g/g}$	52.83 (28/53)	94.44 (68/72)
FC	0.844	0.765 ~ 0.924	241.51 $\mu\text{g/g}$	69.81 (37/53)	97.22 (70/72)
LF	0.830	0.749 ~ 0.912	190.32 $\mu\text{g/g}$	67.92 (36/53)	98.61 (71/72)
联合应用	0.895	0.831 ~ 0.958	上述各自值	88.70 (47/53)	90.28 (65/72)

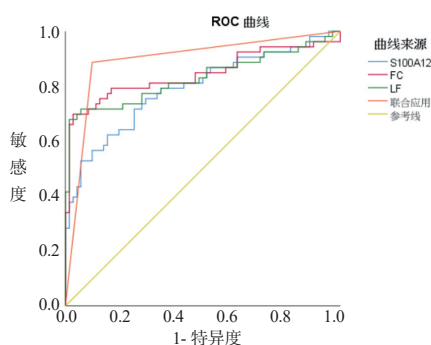


图1 粪便S100A12, FC, LF对UC患者疾病活动度的评估价值

表2 粪便S100A12, FC, LF对UC患者黏膜愈合的评估价值

指标	曲线下面积	95CI%	最佳截断值	敏感度(%)	特异度(%)
S100A12	0.839	0.749 ~ 0.929	0.59 $\mu\text{g/g}$	88.24 (30/34)	68.42 (26/38)
FC	0.801	0.690 ~ 0.912	119.45 $\mu\text{g/g}$	73.53 (25/34)	92.11 (35/38)
LF	0.765	0.647 ~ 0.882	101.28 $\mu\text{g/g}$	61.76 (21/34)	92.11 (35/38)
联合应用	0.890	0.806 ~ 0.974	上述各自值	91.18 (31/34)	86.84 (33/38)

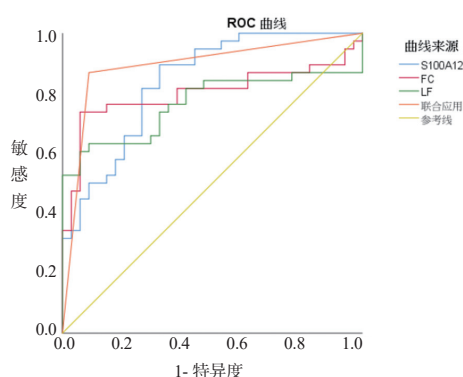


图2 粪便S100A12, FC, LF对UC患者黏膜愈合的评估价值

3 讨论

UC发病机制复杂, 至今尚未能完全阐明, 目前还属于难治愈性疾病, 准确的评估患者的病情有助于临床治疗方案的制定, 利于改善患者的预后^[8]。黏膜愈合是炎症性肠病国际组织在2007年提出的概念, 定义为肠道黏膜所有可视化部分无易碎性、出血、糜烂和溃疡^[9], 近年来临床试验研究表明^[10],

2.5 粪便S100A12, FC和LF对UC患者黏膜愈合的评估价值 见表2, 图2。以黏膜愈合组患者的数据为阳性样本, 以黏膜病变组患者的数据为阴性样本, 采用ROC分析粪便S100A12, FC和LF对UC患者黏膜愈合的评估价值。结果显示, 粪便S100A12, FC对UC患者黏膜愈合的评估价值较高, 曲线下面积均在0.8以上, 而LF的评估价值稍低, 曲线下面积为0.765。三者联合应用可进一步提高对UC患者黏膜愈合的评估价值, 曲线下面积可提升至0.890, 敏感度和特异度分别为91.18%, 86.84%。

黏膜愈合是一项可靠的治疗目标, 因此准确地评估UC患者的黏膜愈合情况具有重要的临床价值。近年来有大量与UC相关的生物标志物被发现, 部分血清炎症标志物虽可在一定程度上反映UC患者的病情, 但其表达水平易受到全身炎症状态的影响, 特异度及灵敏度较差。粪便生物标志物是目前评估UC患者病情的重要指标, 由于粪便与肠道黏膜直接接触, 受其他因素的影响较小, 因此可较好地反映肠道黏膜炎症状况^[11-12], 因此本研究着重分析了粪便生物标志物与UC患者黏膜愈合的关系。

本研究结果显示, 活动组的粪便S100A12, FC和LF水平明显高于缓解组, 黏膜病变组的粪便S100A12, FC和LF水平明显高于黏膜愈合组, 且粪便S100A12, FC和LF水平与UCEIS评分均呈正相关, 这提示三种粪便生物标志物均与UC患者的疾病活动度以及黏膜愈合情况存在一定的关系。S100A12是S100蛋白家族成员之一, 是一种促炎性反应的钙结合蛋白, 可参与机体的免疫防御以及炎症反应^[13]。S100A12主要由粒细胞分泌,

主要表达于中性粒细胞中,在UC发生、发展的过程中,中性粒细胞异常活化,且肠黏膜中有大量中性粒细胞的聚集,这导致S100A12分泌增加^[14]。HEIDA等^[15]人的研究发现,初诊的炎症性肠病患者以及青少年炎症性肠病患者的粪便S100A12的表达水平高于健康人群,还有相关研究显示^[14],粪便S100A12在UC,克罗恩病、肠易激综合征中均呈异常高表达,但在UC中的表达水平最高。FC,LF均是临床常见的UC生物标志物,FC是由两个异源钙结合蛋白组成的二聚体,亦属于S100蛋白家族,其主要来源于中性粒细胞、单核细胞和巨噬细胞,在肠黏膜出现炎症浸润时会大量分泌^[16-17]。LF属于转铁蛋白家族,在炎症状态下巨噬细胞以及中性粒细胞均可分泌LF,因此其在UC患者血清及粪便中均呈高表达^[18-19]。我国2018版的《炎症性肠病诊断与治疗的共识意见》也建议将FC,LF作为诊断UC的辅助性指标^[7]。

本研究采用ROC分析发现,粪便S100A12,FC和LF对UC患者的疾病活动度以及黏膜愈合均有一定的评估价值,但单一指标检测各有优缺点,如粪便S100A12,FC和LF评估患者疾病活动度时特异度均很高,但敏感度很低,而粪便S100A12在评估患者黏膜愈合情况时敏感度较佳,但特异度又不理想。迄今尚无一种生物标志物可代替传统的内镜检查和病理检查,在此情形下,多项指标联合应用成为一种有效的补充手段。本研究结果显示,粪便S100A12,FC和LF联合应用可有效提高对UC患者疾病活动度和黏膜愈合的评估价值。本研究尚且存在些许不足之处,首选选取的病例数较少,尤其是黏膜愈合组的例数只有34例,可能会导致结果出现一定的偏倚。另一方面未能选取初诊UC病例进行研究,部分纳入研究的UC患者病程较长,有长时间的用药史,可能会对研究结果产生一定的影响。这些不足之处将在后续的研究中加以改进。

综上所述,粪便S100A12,FC和LF联合应用对UC患者疾病活动度和黏膜愈合的评估价值较高,临床可通过检测患者粪便S100A12,FC和LF的表达情况对患者的病情进行有效的评估,具有一定的临床应用价值。

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