

结直肠癌患者血清 IRF5 和 SOCS-3 表达水平对术后肠梗阻的预测价值

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摘要: **目的** 观察结直肠癌患者血清干扰素调节因子-5 (interferon regulatory factor-5, IRF5)、细胞因子信号转导抑制因子-3 (suppressors of cytokine signaling-3, SOCS-3) 水平, 并探讨其水平对患者术后肠梗阻发生的预测价值。**方法** 选取 2022 年 1 月~2023 年 3 月在沧州市人民医院就诊的 100 例结直肠癌患者为研究对象, 根据患者术后是否发生肠梗阻, 将其分为肠梗阻组 ($n=14$) 和对照组 ($n=86$)。酶联免疫吸附 (ELISA) 法检测术前血清 IRF5 和 SOCS-3 水平。采用 Logistic 回归分析结直肠癌患者术后肠梗阻发生的影响因素。采用受试者工作特征 (ROC) 曲线分析血清 IRF5, SOCS-3 水平对结直肠癌患者术后肠梗阻发生的诊断价值。**结果** 肠梗阻组患者血清 IRF5 水平 ($0.68 \pm 0.09\text{ng/ml}$) 低于对照组 ($0.89 \pm 0.12\text{ng/ml}$), 血清 SOCS-3 水平 ($97.23 \pm 15.94\text{pg/ml}$) 高于对照组 ($75.03 \pm 12.46\text{pg/ml}$), 差异具有统计学意义 ($t=6.257, 5.937$, 均 $P < 0.05$)。SOCS-3 是影响结直肠癌患者术后肠梗阻发生的独立危险因素 ($\text{OR}=2.197$, $95\%\text{CI}: 1.167\sim4.138$, $P < 0.05$), IRF5 是影响结直肠癌患者术后肠梗阻发生的独立保护因素 ($\text{OR}=0.823$, $95\%\text{CI}: 0.705\sim0.961$, $P < 0.05$)。血清 IRF5, SOCS-3 以及二者联合诊断结直肠癌患者术后肠梗阻的 ROC 曲线下面积 (AUC) 分别为 0.852 ($95\%\text{CI}: 0.767\sim0.915$), 0.817 ($95\%\text{CI}: 0.727\sim0.887$) 和 0.953 ($95\%\text{CI}: 0.891\sim0.985$), 二者联合诊断效能高于血清 IRF5, SOCS-3 单独检测效能, 差异具有统计学意义 ($Z=1.967, 2.034$, $P=0.049, 0.042$)。**结论** 结直肠癌患者血清 IRF5 水平降低, SOCS-3 水平升高, 且二者对结直肠癌患者发生术后肠梗阻具有一定的预测价值。

关键词: 结直肠癌; 术后肠梗阻; 干扰素调节因子-5; 细胞因子信号转导抑制因子-3

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Predictive Value of Serum IRF5 and SOCS-3 Expression Levels in Colorectal Cancer Patients for Postoperative Intestinal Obstruction

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Abstract: **Objective** To observe serum interferon regulatory factor-5 (IRF5) and suppressors of cytokine signaling-3 (SOCS-3) levels in patients with colorectal cancer, and investigate predictive value of their levels on the occurrence of postoperative intestinal obstruction in patients. **Methods** A total of 100 colorectal cancer patients who attended the Cangzhou People's Hospital from January 2022 to March 2023 were selected as the study subjects. According to whether the patient experienced intestinal obstruction after surgery, they were divided into the intestinal obstruction group ($n=14$) and the control group ($n=86$). Preoperative serum levels of IRF5 and SOCS-3 were detected by enzyme-linked immunosorbent assay (ELISA). Factors influencing the occurrence of postoperative intestinal obstruction in colorectal cancer patients were analyzed by Logistic regression. Receiver operating characteristic (ROC) curve was used to analyze the diagnostic value of serum IRF5 and SOCS-3 levels on the occurrence of postoperative intestinal obstruction in colorectal cancer patients. **Results** Serum IRF5 levels in the intestinal infarction group ($0.68 \pm 0.09\text{ng/ml}$) were lower, but serum SOCS-3 levels in the intestinal infarction group ($97.23 \pm 15.94\text{pg/ml}$) were higher than in the control group ($0.89 \pm 0.12\text{ng/ml}$, $75.03 \pm 12.46\text{pg/ml}$), with significant differences ($t=6.257, 5.937$, all $P < 0.05$). SOCS-3 was an independent risk factor ($\text{OR}=2.197$, $95\%\text{CI}: 1.167\sim4.138$, $P < 0.05$), and IRF5 was an independent protective factor ($\text{OR}=0.823$, $95\%\text{CI}: 0.705\sim0.961$, $P < 0.05$) affecting the occurrence of postoperative bowel obstruction in patients with colorectal cancer. The areas under the curve (AUC) of serum IRF5, SOCS-3, and the

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combination of the two for the diagnosis of postoperative intestinal obstruction in colorectal cancer patients were 0.852 (95%CI: 0.767~0.915), 0.817 (95%CI: 0.727~0.887) and 0.953 (95%CI: 0.891~0.985), respectively. The combined diagnostic efficacy of the serum IRF5, SOCS-3 was higher than the efficacy of the test alone, with significant differences ($Z=1.967, 2.034, P=0.049, 0.042$). **Conclusion** Serum IRF5 levels are reduced, but SOCS-3 levels are increased in patients with colorectal cancer. Both have a predictive value for the development of postoperative bowel obstruction in patients with colorectal cancer.

Keywords: colorectal cancer; postoperative intestinal obstruction; interferon regulatory factor-5; suppressors of cytokine signaling-3

结直肠癌 (colorectal cancer) 是消化系统方面常见的恶性肿瘤, 其发病率和死亡率都较高^[1]。结直肠癌患者的临床症状通常表现为便血、大便不成型、消瘦等, 而术后肠梗阻则是患者在术后可能发生的并发症之一^[2-3]。术后肠梗阻容易导致患者出现恶心呕吐、肛门排便排气困难、腹痛腹胀等不良症状, 严重影响患者的术后恢复^[3]。因此, 寻找影响结直肠癌患者术后肠梗阻的常用指标, 对于结直肠癌患者术后肠梗阻的防治具有重要意义。干扰素调节因子-5 (interferon regulatory factor 5, IRF5) 是干扰素调节因子家族的成员, 能够参与调节多种恶性肿瘤的发生及发展^[4]。报道显示, IRF5 在多种癌组织中均表现出低水平, 且 IRF5 低表达可以促进肠道炎症的发生^[5-7]。细胞因子信号转导抑制因子-3 (suppressor of cytokine signaling 3, SOCS-3) 的高表达与某些代谢性疾病、细菌和病毒感染有关^[8]。血清 IRF5, SOCS-3 在结直肠癌患者发生术后肠梗阻方面的临床价值尚不清楚。因此, 本研究主要探讨血清 IRF5, SOCS-3 水平与结直肠癌患者发生术后肠梗阻之间的关系, 为结直肠癌患者术后肠梗阻的预防及治疗提供参考。

1 材料与方法

1.1 研究对象 本研究经过沧州市人民医院伦理委员会批准, 选取 2022 年 1 月~2023 年 3 月在沧州市人民医院就诊的 100 例结直肠癌患者为研究对象, 根据患者术后是否发生肠梗阻, 将其分为肠梗阻组 ($n=14$) 和对照组 ($n=86$)。纳入标准: ①符合结直肠癌病理学诊断标准^[9]且接受手术治疗; ②术前未进行抗肿瘤治疗; ③临床资料完整; ④患者或近亲属知情同意。排除标准: ①近三个月内接受过手术治疗; ②并发严重消化系统疾病; ③并发其它恶性肿瘤; ④放弃治疗者。

1.2 仪器与试剂 IRF5 试剂盒 (货号: ZY-IRF5-Hu, 上海泽叶生物科技有限公司); SOCS-3 试剂盒 (货号: ml023834, 上海酶联生物科技有限公司); 酶标仪 (型号: PR4100, 美国 Bio-Rad 公司)。

1.3 方法

1.3.1 临床资料收集: 收集结直肠癌患者的临床资料, 主要包括性别、年龄 (≥ 60 岁, < 60 岁)、肿瘤直径 (≥ 5 cm, < 5 cm)、肿瘤位置 (直肠,

结肠)、TNM 分期 (I~II 期, III~IV 期)、身体质量指数 (BMI, ≥ 24 kg/m², < 24 kg/m²)、手术方式 (腹腔镜, 开腹)、手术时间 (≥ 2.5 h, < 2.5 h)、吸烟史 (有, 无) 及饮酒史 (有, 无) 等。

1.3.2 结直肠癌患者血清 IRF5, SOCS-3 水平检测: 采集结直肠癌患者术前静脉血标本, 离心收集上层血清, 置于 -80°C 下保存, 以供后续检测。采用酶联免疫吸附 (enzyme linked immunosorbent assay, ELISA) 法检测结直肠癌患者血清 IRF5, SOCS-3 水平, 具体操作严格按照说明书执行。

1.4 统计学分析 选择 SPSS 25.0 对本研究全部检测指标进行统计学分析。计数资料以 n (%) 表示, 组间比较采用卡方 (χ^2) 检验; 计量资料符合正态分布, 以均数 \pm 标准差 ($\bar{x} \pm s$) 表示, 两组之间比较选择独立样本 t 检验。采用 Logistic 回归分析法对结直肠癌患者术后肠梗阻发生的影响因素进行分析。采用受试者工作特征 (receiver operating characteristic, ROC) 曲线分析血清 IRF5, SOCS-3 水平对结直肠癌患者术后肠梗阻发生的诊断价值。 $P < 0.05$ 为差异具有统计学意义。

2 结果

2.1 肠梗阻和对照组血清 IRF5, SOCS-3 水平比较 肠梗阻组血清 IRF5 表达水平低于对照组 (0.68 ± 0.09 ng/ml vs 0.89 ± 0.12 ng/ml), 血清 SOCS-3 水平高于对照组 (97.23 ± 15.94 pg/ml vs 75.03 ± 12.46 pg/ml), 差异具有统计学意义 ($t=6.257, 5.937$, 均 $P < 0.001$)。

2.2 肠梗阻与对照组临床资料比较 见表 1。肠梗阻组 TNM 分期 III~IV 期、手术时间 ≥ 2.5 h 的结直肠癌患者比例显著高于对照组 ($P < 0.05$); 肠梗阻组与对照组年龄、性别、肿瘤直径、肿瘤位置、BMI, 手术方式、吸烟史和饮酒史比较, 差异均无统计学意义 ($P > 0.05$)。

2.3 影响结直肠癌患者术后肠梗阻发生的多因素分析 见表 2。以结直肠癌患者术后肠梗阻发生情况为因变量 (发生 = 1, 未发生 = 0), 血清 IRF5, SOCS-3 水平、TNM 分期及手术时间为自变量进行 Logistic 多因素回归分析, 结果显示, 影响结直肠癌患者术后肠梗阻发生的独立危险因素为 SOCS-3, 而 IRF5 则是影响结直肠癌患者术后肠梗阻发生

的保护因素 ($P < 0.05$)。

| 表 1 肠梗阻组和对照组临床资料指标比较 [n (%)] | | | | | | |
|--------------------------------|------------|------------|------------|------------|-------|--|
| 类 别 | n | 肠梗阻 (n=14) | 对照组 (n=86) | χ^2 值 | P 值 | |
| 年龄 (岁) | ≥ 60 | 58 | 9 (64.29) | 0.264 | 0.607 | |
| | < 60 | 42 | 5 (35.71) | | | |
| 性别 | 男 | 52 | 8 (57.14) | 0.173 | 0.678 | |
| | 女 | 48 | 6 (42.86) | | | |
| 肿瘤直径 (cm) | ≥ 5 | 53 | 8 (57.14) | 0.112 | 0.738 | |
| | < 5 | 47 | 6 (42.86) | | | |
| 肿瘤位置 | 直肠 | 59 | 9 (64.29) | 0.188 | 0.665 | |
| | 结肠 | 41 | 5 (35.71) | | | |
| TNM 分期 | I ~ II 期 | 68 | 4 (28.57) | 11.630 | 0.001 | |
| | III ~ IV 期 | 32 | 10 (71.43) | | | |
| BMI (kg/m ²) | ≥ 24 | 51 | 6 (42.86) | 0.432 | 0.511 | |
| | < 24 | 49 | 8 (57.14) | | | |
| 手术方式 | 腹腔镜手术 | 46 | 7 (50.00) | 0.105 | 0.746 | |
| | 开腹手术 | 54 | 7 (50.00) | | | |
| 手术时间 (h) | ≥ 2.5 | 54 | 11 (78.57) | 3.957 | 0.047 | |
| | < 2.5 | 46 | 3 (21.43) | | | |
| 吸烟史 | 有 | 46 | 8 (57.14) | 0.814 | 0.367 | |
| | 无 | 54 | 6 (42.86) | | | |
| 饮酒史 | 有 | 52 | 9 (64.29) | 0.984 | 0.321 | |
| | 无 | 48 | 5 (35.71) | | | |

| 表 2 影响结直肠癌患者术后肠梗阻发生的多因素 Logistic 分析 | | | | | | |
|-------------------------------------|--------|-------|---------------|-------|-------------|-------|
| 因素 | β | SE | Wald χ^2 | OR | 95%CI | P |
| IRF5 | -0.195 | 0.079 | 6.080 | 0.823 | 0.705~0.961 | 0.014 |
| SOCS-3 | 0.787 | 0.323 | 5.938 | 2.197 | 1.167~4.138 | 0.015 |
| TNM 分期 | 0.680 | 0.359 | 3.588 | 1.974 | 0.977~3.990 | 0.058 |
| 手术时间 | 0.616 | 0.391 | 2.484 | 1.852 | 0.861~3.985 | 0.115 |

2.4 血清 IRF5, SOCS-3 水平对结直肠癌术后肠梗阻的诊断价值 分别以结直肠癌患者术后血清 IRF5, SOCS-3 水平的单独检测值以及二者联合预测概率值为检验变量, 以患者术后是否出现肠梗阻为状态变量绘制 ROC 曲线, 见图 1。血清 IRF5, SOCS-3 以及二者联合诊断结直肠癌患者术后肠梗阻的 ROC 曲线下面积 (area under the curve, AUC) 分别为 0.852, 0.817 和 0.953, 血清 IRF5, SOCS-3 联合诊断效能高于单独检测效能 ($Z=1.967$, 2.034 , $P=0.049$, 0.042), 见表 3。

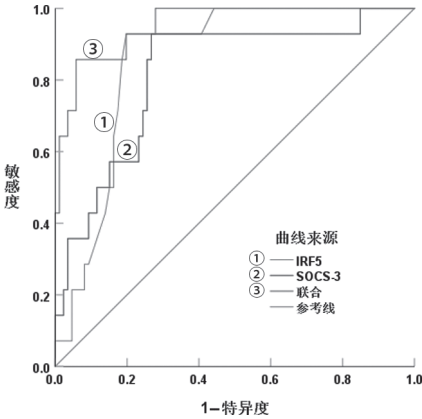


图 1 血清 IRF5, SOCS-3 水平预测结直肠癌术后肠梗阻的 ROC 曲线

表3 血清 IRF5, SOCS-3 水平对结直肠癌术后肠梗阻的诊断效能分析

| 项目 | AUC | 95%CI | 截断值 | 敏感度 (%) | 特异度 (%) | 约登指数 |
|--------|-------|-------------|-------------|---------|---------|-------|
| IRF5 | 0.852 | 0.767~0.915 | 0.75 ng/ml | 92.86 | 80.23 | 0.731 |
| SOCS-3 | 0.817 | 0.727~0.887 | 82.06 pg/ml | 92.86 | 73.26 | 0.661 |
| 联合诊断 | 0.953 | 0.891~0.985 | - | 85.71 | 94.19 | 0.799 |

3 讨论

结直肠癌是一种常见的消化系统恶性肿瘤,多发于中老年群体,其发病率和死亡率都较高^[10]。结直肠癌患者早期症状不明显,而在中晚期通常表现出便血、大便不成型、腹痛、消瘦等症状,甚至还可能引起术后肠梗阻等并发症^[11-12]。术后肠梗阻主要是由于结直肠癌患者手术后胃肠道恢复延迟,阻碍肠道内容物顺利通过,从而导致患者出现恶心呕吐、停止排便排气、腹痛腹胀、肠鸣音异常等症状,甚至造成胃肠道脱水和脓毒血症等严重症状^[13]。结直肠癌患者发生术后肠梗阻,不仅对自身的生命健康造成了极大威胁,且由于治疗时间及治疗费用的增加,对患者的家庭经济状况也造成了极大负担。因此,寻找影响结直肠癌患者发生术后肠梗阻的常用生物学指标,对于结直肠癌患者术后肠梗阻的防治具有重要意义。

IRF 属于转录因子家族,可以参与干扰素转录过程,在免疫调控及细胞分化方面能够发挥重要功能^[14]。IRF5 属于干扰素调节因子的一种,一般表达于机体的淋巴组织中,在机体免疫防御方面发挥重要作用,能够参与调节多种肿瘤的发生及发展^[15]。BI 等^[16]的研究发现,IRF5 在乳腺癌组织中表现出低水平,且当 IRF5 呈现高表达时,能够抑制乳腺癌细胞株的增殖及侵袭。高飞等^[17]的研究发现,鼻咽癌组织中 IRF5 水平较癌旁组织显著降低。报道显示 IRF5 低表达可以促进巨噬细胞 M1 型分化,从而加重肠道炎症^[18]。本研究显示,结直肠癌患者术后发生肠梗阻血清 IRF5 表达水平显著低于对照组,提示 IRF5 低水平与结直肠癌术后肠梗阻的发生及发展有重要联系,分析其原因,结肠癌患者术后低水平 IRF5 会促使患者巨噬细胞活化,引起大量炎症细胞因子渗出,进而导致消化道组织水肿、酸碱平衡失调以及电解质紊乱引发肠梗阻^[18-19]。进一步 Logistic 多因素回归分析结果显示,IRF5 则是影响结直肠癌患者术后肠梗阻发生的独立保护因素,且血清 IRF5 诊断结直肠癌患者术后肠梗阻的 AUC 为 0.852,敏感度和特异度分别为 92.86%,80.23%,提示 IRF5 对结肠癌患者术后发生肠梗阻具有一定的诊断价值,临床上可对 IRF5 低水平患者制定针对性治疗方案,以降低术后肠梗阻的发生,改善患者预后。

SOCS-3 属于 SOCS 蛋白的一种,在肠道中多

有分布,其可以通过调节细胞因子介导的炎症信号(如 IL-6, IL-10, TNF- α , TNF- γ 等)来控制先天和获得性免疫反应^[20-21]。研究发现由于所处的细胞环境不同,SOCS-3 既可以作为致癌基因,也可以作为肿瘤抑制因子,而 SOCS-3 的高表达往往与一些代谢性疾病或某些细菌和病毒感染的免疫逃避有关^[22-23]。朱东东等^[24]的研究显示,肠道菌群失调可促进炎症反应,使炎症因子水平升高,而炎症因子水平异常又会导致 SOCS-3 呈现高表达。本研究显示,结直肠癌患者术后发生肠梗阻血清 SOCS-3 水平显著高于对照组,提示 SOCS-3 高表达与结直肠癌术后肠梗阻的发生及发展密切相关,分析其原因,高水平 SOCS-3 可能会引起结直肠癌术后患者免疫失衡,使促炎因子水平升高而引发腹腔内术后炎症性粘连及肠道炎症水肿,最终导致肠梗阻的发生^[24]。进一步 Logistic 多因素回归分析发现 SOCS-3 是影响结直肠癌患者术后肠梗阻发生的独立危险因素,且 ROC 曲线分析发现血清 SOCS-3 诊断结直肠癌患者术后肠梗阻的 AUC 为 0.817,敏感度和特异度分别为 92.86%,73.26%,提示 SOCS-3 可作为结肠癌患者术后发生肠梗阻的有价值的诊断标志物,监测患者 SOCS-3 水平对降低结肠癌患者术后肠梗阻的发生具有一定的临床价值。

另外本研究还发现血清 SOCS-3, IRF5 及二者联合在预测结直肠癌患者术后肠梗阻的发生方面具有一定诊断价值,且联合诊断效能高于二者单独检测效能,提示 SOCS-3, IRF5 可预测结直肠癌患者术后肠梗阻的发生情况,具有一定临床应用价值。

综上所述,结直肠癌患者血清 IRF5 水平降低,SOCS-3 水平升高,且二者对结直肠癌患者发生术后肠梗阻具有一定的预测价值。此外,本研究所选择样本量较少,可能造成统计结果的偏差,今后将进行前瞻性的大样本研究,进一步证实血清 IRF5, SOCS-3 在结直肠癌患者术后肠梗阻诊断中的价值,并深入探究二者在结直肠癌患者术后肠梗阻的作用机制。

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