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血清 DR–70 联合 CEA、CA199 对结直肠癌的诊断价值

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[摘　要]　**目的：**探讨血清纤维蛋白降解复合物DR-70联合癌胚抗原(carcinoembryonic antigen，CEA)、糖类抗原199(carbohydrate antigen 199，CA199)对结直肠癌的诊断价值。**方法：**选取2018年1月至2021年6月阜阳市第五人民医院收治的结直肠癌患者200例，另选取良性结直肠病变患者100例及健康体检者100名，均采血检测血清DR-70及CEA、CA199水平。比较各组血清DR-70及CEA、CA199水平，并采用受试者工作特征(receiver operating characteristic，ROC)曲线评价各指标对结直肠癌的诊断效能，分析DR-70与结直肠癌临床病理参数的关系，并观察结直肠癌患者手术前后血清DR-70水平变化。**结果：**结直肠癌患者血清DR-70水平为(1.15±0.39) μg/mL，显著高于良性结直肠病变患者的(0.47±0.10) μg/mL和健康体检者的(0.46±0.12) μg/mL，差异均有统计学意义(P<0.05)；并且结直肠癌患者血清CEA、CA199也显著增高(P<0.05)。ROC曲线分析显示DR-70、CEA、CA199诊断结直肠癌的曲线下面积分别为0.838、0.805、0.622，三者联合诊断的曲线下面积为0.919，优于各单一检测(P<0.05)。在结直肠癌患者中，III+IV期患者血清DR-70水平显著高于I+II期，并且低分化程度患者血清DR-70水平显著高于中高分化(P<0.05)；并且结直肠癌患者术后血清DR-70水平相比术前显著降低，差异有统计学意义(P<0.05)。**结论：**结直肠癌患者血清DR-70水平显著增高，DR-70可作为结直肠癌筛查的潜在标志物，联合CEA、CA199可提高诊断效果。

[关键词]　结直肠癌；诊断；纤维蛋白降解复合物；癌胚抗原；糖类抗原199

Diagnostic value of serum DR-70 combined with CEA and CA199 in colorectal cancer

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Abstract　**Objective:** To investigate the diagnostic value of serum fibrin degradation complex (DR-70) combined with carcinoembryonic antigen (CEA) and carbohydrate antigen 199 (CA199) in colorectal cancer. **Methods:** A total of 200 patients with colorectal cancer admitted to Fuyang Fifth People's Hospital from January 2019 to June 2021 were selected, and 100 patients with benign colorectal lesions and 100 healthy subjects were selected. Serum DR-70, CEA and CA199 levels were detected. The serum levels of DR-70, CEA and CA199 in each group were compared, and the diagnostic efficacy of each index for colorectal cancer was evaluated by receiver operating

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characteristic curve (ROC). The relationship between DR-70 and clinicopathological parameters of colorectal cancer was analyzed, and the changes of serum DR-70 levels before and after surgery in patients with colorectal cancer were observed. **Results:** The serum DR-70 level in patients with colorectal cancer was (1.15±0.39) μg/mL, which was higher than (0.47±0.10) μg/mL in patients with benign colorectal lesions and (0.46±0.12) μg/mL in healthy subjects, and the differences were statistically significant (P<0.05). The serum CEA and CA199 in patients with colorectal cancer were also significantly increased (P<0.05). ROC curve analysis showed that the area under the curve of DR-70, CEA and CA199 in the diagnosis of colorectal cancer was 0.838, 0.805 and 0.622, respectively. The area under the curve of the combined diagnosis of the three was 0.919, which was better than that of the single detection (P<0.05). In patients with colorectal cancer, the serum DR-70 level in stage III+IV patients was significantly higher than that in stage I+II patients, and the serum DR-70 level in patients with low differentiation was significantly higher than that in patients with medium and high differentiation (P<0.05). The postoperative serum DR-70 level in patients with colorectal cancer was lower than that before operation, and the difference was statistically significant (P<0.05). **Conclusion:** The serum level of DR-70 in patients with colorectal cancer is significantly increased. DR-70 can be used as a potential marker for colorectal cancer screening, and combined with CEA and CA199 can improve the diagnostic efficacy.

Keywords colorectal cancer; diagnosis; fibrin degradation complex; carcinoembryonic antigen; carbohydrate antigen 199

结直肠癌是临床常见的消化道恶性肿瘤，其发病率居所有癌症的第3位，病死率居第2位[1]。由于结直肠癌起病隐匿、进展迅速，多数患者诊断时已处于晚期，故早期筛查和诊断尤为重要。目前，癌胚抗原(carcinoembryonic antigen，CEA)、糖类抗原199(carbohydrate antigen 199，CA199)等血清肿瘤标志物已在结直肠癌诊治中得以应用，但筛查效果欠佳[2-3]，探讨新型生物标志物以提高筛查效果有着重要意义。DR-70是纤维蛋白降解复合物。研究[4]表明：肿瘤细胞能够促进凝血因子等释放，致使机体处于血液高凝状态，引起纤维蛋白原和纤维蛋白增多；并且肿瘤细胞能够通过合成纤溶酶原激活物(plasminogen activator，PA)，降解纤维蛋白原和纤维蛋白，从而使得血清DR-70水平升高。研究[5-6]显示：纤维蛋白降解产物(fibrin degradation product，FDP)与肿瘤的发生和发展具有相关性。本研究旨在检测结直肠癌患者血清DR-70水平，探讨其联合CEA、CA199对结直肠癌早期筛查的诊断效能。

1 对象与方法

1.1 对象

选取2018年1月至2021年6月阜阳市第五人民医院收治的结直肠癌患者。纳入标准：1)经病理学确诊为结直肠癌；2)入院前未接受任何抗肿瘤治疗；3)临床资料完整。排除标准：1)伴其他恶性肿瘤；2)心、肝、肾功能严重损伤；3)有血液系统疾病；4)有抗凝药物长期应用史；5)明确诊断为心脑血管疾病。共纳入200例(病例组)，其中直肠癌82例，结肠癌118例；男129例，女71例，年龄24~75(59.01±11.49)岁。临床分期：I期50例，II期54例，III期69例，IV期27例。选取同期阜阳市第五人民医院收治的良性结直肠病变患者100例(良性病变组)，心、肝、肾功能均正常，排除其他恶性肿瘤，其中男59例，女41例，年龄23~75(58.39±10.74)岁。另选取同期在阜阳市第五人民医院体检中心接受体检的健康体检者100例(健康对照组)，均排除结直肠病变，无其他任何肿瘤，无血液系统疾病，其中男52例，女48例，年龄20~75(58.57±11.77)岁。3组性别、年龄等一般资料比较差异无统计学意义(P>0.05)。本研究通过阜阳市第五人民医院医学伦理委员会审批，采集标本时患者均签署知情同意书。

1.2 方法

清晨抽取患者空腹静脉血3 mL，置于标准分离管中，严格无菌操作。室温下静置1 h，离心10 min (3 000 r/min，r=13.5 cm)，分离得到血清，放置到−20 ℃环境下保存待测。采用电化学发光法进行CEA、CA199的检测，仪器及配套试剂盒为德国罗氏诊断有限公司产品；采用酶联免疫吸附法检测DR-70水平，试剂盒购自宁波瑞源生物科技有限公

司；检测严格执行试剂盒说明书步骤；良性病变组于治疗前检测1次，健康对照组于体检时检测1次，结直肠癌患者于手术前后各检测1次(IV期患者行原发灶和转移灶同期手术切除，原发灶及肝转移灶均实现R0切除)。

1.3 统计学处理

采用SPSS24.0进行数据处理。正态分布的计量资料采用均数±标准差($\bar{x}\pm s$)进行描述，两组间比较用独立样本t检验，多组间比较用单因素方差分析；通过logistic回归分析构建DR-70、CEA、CA199的联合诊断模型；并采用受试者工作特征(receiver operating characteristic，ROC)曲线评价DR-70、CEA、CA199及联合模型对结直肠癌的诊断价值；以P<0.05为差异有统计学意义。

2 结果

2.1 3组血清DR-70、CEA、CA199水平比较

病例组(术前)血清DR-70、CEA、CA199水平均显著高于良性病变组和健康对照组(P<0.05，表1)。

2.2 血清DR-70、CEA、CA199诊断结直肠癌的ROC曲线

ROC曲线分析显示：DR-70、CEA、CA199及联诊合断模型诊断结直肠癌的曲线下面积分别为0.838、0.805、0.622和0.919，以联合诊断的曲线下面积最大(表2，图1)。

2.3 血清DR-70与结直肠癌临床病理参数的关系

在结直肠癌患者中，III+IV期患者血清DR-70水平显著高于I+II期，并且低分化程度患者血清DR-70水平显著高于中高分化，差异有统计学意义(P<0.05)；而血清DR-70水平与性别、年龄、肿瘤直径无明显相关性(P>0.05，表3)。

2.4 血清DR-70在结直肠癌患者手术前后的变化

200例结直肠癌患者术前血清DR-70水平为(1.15±0.39) μg/mL，术后血清DR-70水平为(0.98±0.28) μg/mL，术后相比术前显著降低，差异有统计学意义(t=3.210，P=0.002)。

表1 3组血清DR-70、CEA、CA199水平比较

Table 1 Comparison of serum DR-70, CEA and CA199 levels between the 3 groups

组别	n	DR-70/(μg·mL^{-1})	CEA/(μg·L^{-1})	CA199/(U·mL^{-1})
病例组(术前)	200	1.15 ± 0.39^{ab}	29.34 ± 9.14^{ab}	111.09 ± 35.44^{ab}
良性病变组	100	0.47 ± 0.10	12.21 ± 4.24^{a}	44.34 ± 12.94^{a}
健康对照组	100	0.46 ± 0.12	4.73 ± 1.34	17.32 ± 4.89
F		26.214	76.584	110.547
P		<0.001	<0.001	<0.001

与健康对照组相比，^{a}P<0.05；与良性病变组相比，^{b}P<0.05。

Compared with the healthy control group, ^{a}P<0.05; compared with benign lesion group, ^{b}P<0.05.

表2 DR-70、CEA、CA199及其联合对结直肠癌的诊断效能

Table 2 Diagnostic efficacy of DR-70, CEA, CA199 and their combination in colorectal cancer

项目	最佳截断值	AUC	P	95%CI	敏感度/%	特异度/%
DR-70	0.97 μg/mL	0.838	<0.001	0.773~0.891	66.5	93.5
CEA	22.61 μg/L	0.805	<0.001	0.737~0.863	69.5	83.0
CA199	82.16 U/mL	0.622	<0.001	0.544~0.670	82.0	43.0
三者联合		0.919	<0.001	0.866~0.956	80.5	93.5

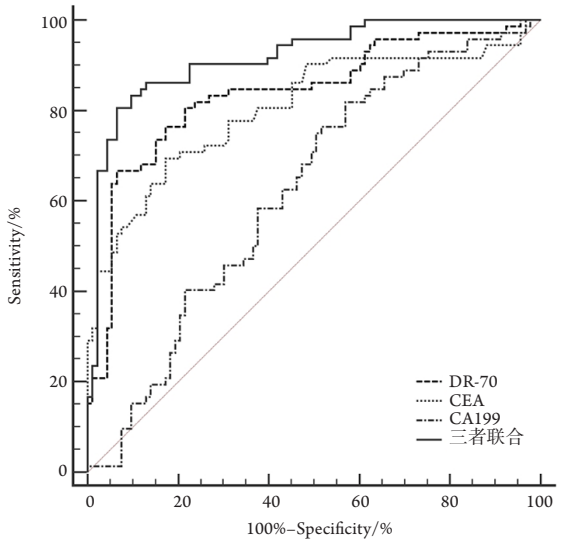

图1 血清DR-70、CEA、CA199诊断结直肠癌的ROC曲线

Figure 1 ROC curve of serum DR-70, CEA, and CA199 in diagnosis of colorectal cancer

表3 血清DR-70水平与结直肠癌临床病理参数的关系

Table 3 Relationship between serum DR-70 level and clinicopathological parameters of colorectal cancer

临床病理参数	*n*	DR-70水平/(μg·mL^{-1})	*t*	*P*
性别			1.256	0.210
男	129	1.17 ± 0.33		
女	71	1.11 ± 0.31		
年龄/岁			1.321	0.188
<50	43	1.09 ± 0.32		
≥50	157	1.17 ± 0.36		
肿瘤直径/cm			1.386	0.167
<4	83	1.11 ± 0.34		
≥4	117	1.18 ± 0.36		
临床分期			3.129	0.002
I+II	104	1.08 ± 0.31		
III+IV	96	1.23 ± 0.35		
分化程度			2.768	0.006
低分化	131	1.20 ± 0.35		
中高分化	69	1.06 ± 0.32		

3 讨论

结直肠癌的早期筛查有助于降低患者病死率，已成为现阶段研究的重点。目前，临床上肠镜和活检是结直肠癌筛查的金标准，其准确度高，但由于具有侵袭性，难以被患者接受，推广难度大。外周血生物标志物有着检测方便、相对无创、经济的优点，更易受到患者青睐，便于推广实施。传统血清肿瘤标志物CEA、CA199在结直肠癌诊治中已得到广泛应用，但筛查的效能尚不

足。本研究显示：CEA诊断结直肠癌的敏感度为69.5%，特异度为83.0%，CA199敏感度为82.0%，特异度为43.0%，与既往报道[7]接近。因此，寻找新型的生物诊断标志物成为研究之热点。

研究[8]表明：肿瘤形成过程中会伴随着血管新生，并产生大量凝血因子，致使机体处于血液高凝状态。外源性凝血级联反应激活被认为与肿瘤的生长、侵袭有关。纤维蛋白的沉积、溶解在肿瘤增殖、转移中有着重要作用。FDP可促进血管生成，并具有抗炎作用。研究[9]发现癌症患者血清FDP表达显著增高。何小艳等[10]研究表明：血清FDP对肺癌诊断有一定价值，能够反映肿瘤进展。李敏等[11]研究显示：胃癌患者血清FDP水平显著增高，经治疗后显著降低，且与肝转移密切相关。但在传统的FDP检测中，仅部分降解产物被检测出，而本研究中的DR-70检测能够检测出与恶性肿瘤相关的所有FDP产物，更能反映机体凝血、纤溶状况。本研究显示，结直肠癌患者血清DR-70显著高于良性病变组和健康对照组，与Saridemir等[6]报道一致，提示血清DR-70可能与结直肠癌的发生相关；ROC曲线分析显示，血清DR-70诊断结直肠癌的曲线下面积为0.838，敏感度为66.5%，特异度为93.5%，表明DR-70可作为结直肠癌肿瘤筛查的生物标志物。

本研究还显示：不同临床分期患者血清DR-70水平有差异，III+IV期患者血清DR-70水平显著高于I+II期，这与Sari等[12]报道的血清DR-70水平与结直肠癌分期具有相关性的研究结果一致，提示血清DR-70水平与结直肠癌的疾病进展相关，随着病情进展，血清DR-70水平显著增高。在本研究中，分化程度较差的结直肠癌血清DR-70水平显著高于分化程度较好的结直肠癌，提示血清DR-70水平与结直肠癌分化程度相关，结直肠癌恶性程度越高，其血清DR-70水平也越高。另外，通过对结直肠癌患者手术前后血清DR-70水平进行检测，发现患者术后血清DR-70水平显著低于术前。这些结果表明DR-70可能参与了结直肠癌的发生和发展。

临床实践[13-15]证明：单一肿瘤标志物在结直肠癌诊断中的效能欠佳，联合多种肿瘤标志物有助于提高诊断效能。本研究显示，DR-70联合CEA、CA199诊断的曲线下面积为0.919，优于各单一检测，提高了诊断效能。本研究存在局限性：首先，属于单中心、小样本量研究，其所得结果仍需更大样本量研究进行验证；其次，未探讨结直肠癌患者血清DR-70变化的确切机制，以及能否将其作为疗效监测和复发评估的指标，这有待进一步深入观察。

综上，DR-70水平在结直肠癌患者血清中显著升高，可能参与了肿瘤的发生和发展。DR-70可作为结直肠癌筛查的潜在生物标志物，有效弥补CEA、CA199在结直肠癌筛查中的不足，联合应用能够提高诊断效能。

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