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·论　著·

结直肠癌肝转移患者的血浆胆汁酸谱特征及临床价值

贾　茹[1]，张平平[1]，袁　苑[2]，王　炎[1]，冯　琴[3,4,5,6*]
1. 上海中医药大学附属曙光医院肿瘤科，上海 201203
2. 上海中医药大学中西医结合学院，上海 201203
3. 上海中医药大学肝病研究所，上海 201203
4. 上海市中医临床重点实验室，上海 201203
5. 上海中医药大学肝肾疾病病证教育部重点实验室，上海 201203
6. 上海中医药大学附属曙光医院科技实验中心，上海 201203

［**摘要**］ **目的**　分析不同转移情况结直肠癌患者血浆胆汁酸含量及胆汁酸谱分布的差异，并评估血浆胆汁酸含量比值联合肿瘤标志物对结直肠癌肝转移的诊断价值。**方法**　纳入 2021 年 4 月至 2022 年 1 月于上海中医药大学附属曙光医院就诊的结直肠腺癌肝转移或无转移患者 163 例，其中无转移组 82 例、肝转移组 81 例。收集患者的临床资料，用 Karnofsky 功能状态（KPS）评分评估生存质量；收集患者外周血样本，检测总胆汁酸及肿瘤标志物［癌胚抗原（CEA）和糖类抗原 125（CA125）］水平，用高效液相色谱－串联质谱法检测血浆中 15 种胆汁酸的含量。分析两组患者胆汁酸含量及胆汁酸谱分布的差异，并绘制 ROC 曲线分析胆汁酸含量比值联合肿瘤标志物对结直肠癌肝转移的临床诊断效能。**结果**　两组结直肠癌患者年龄、性别、肿瘤位置、病理分化程度、KPS 评分差异无统计学意义（均 $P>0.05$）。肝转移组患者总胆汁酸、CEA、CA125 均较无转移组患者升高（均 $P<0.001$），血浆胆汁酸谱中甘氨胆酸、脱氧胆酸、牛磺脱氧胆酸、甘氨脱氧胆酸、甘氨熊脱氧胆酸、石胆酸和甘氨石胆酸含量均较无转移组患者升高（均 $P<0.05$），血浆次级胆汁酸含量高于无转移组患者（$P<0.001$），次级胆汁酸与初级胆汁酸含量比值高于无转移组患者（$P<0.001$）。次级胆汁酸与初级胆汁酸含量比值联合 CEA、CA125 诊断结直肠癌肝转移的灵敏度为 71.60%，特异度为 80.49%，AUC 为 0.820（95% *CI* 0.754～0.885，$P<0.001$）。**结论**　结直肠癌肝转移患者血浆胆汁酸含量升高，胆汁酸谱异于无转移患者；次级胆汁酸与初级胆汁酸含量比值联合 CEA、CA125 对结直肠癌肝转移有较高的诊断价值。

［**关键词**］ 结直肠肿瘤；肝转移；胆汁酸；次级胆汁酸；诊断标志物
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Characteristic and clinical value of plasma bile acid profile in patients with colorectal cancer liver metastasis

JIA Ru[1], ZHANG Pingping[1], YUAN Yuan[2], WANG Yan[1], FENG Qin[3,4,5,6*]
1. Department of Medical Oncology, Shuguang Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai 201203, China
2. School of Integrative Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai 201203, China
3. Institute of Liver Diseases, Shanghai University of Traditional Chinese Medicine, Shanghai 201203, China
4. Shanghai Key Laboratory of Traditional Chinese Clinical Medicine, Shanghai 201203, China
5. Key Laboratory of Liver and Kidney Diseases, Shanghai University of Traditional Chinese Medicine, Ministry of Education, Shanghai 201203, China
6. Central Laboratory, Shuguang Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai 201203, China

［**Abstract**］ **Objective**　To analyze the differences in plasma bile acid (BA) concentrations and BA profile in colorectal cancer patients with varying metastatic conditions, and to evaluate the clinical value of plasma BA ratio combined

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［**作者简介**］ 贾　茹，主治医师. E-mail: jiaru2468@163.com
*通信作者（Corresponding author）. Tel: 021-20256526, E-mail: fengqin@shutcm.edu.cn

with tumor markers in diagnosing colorectal cancer liver metastasis (CRC-LM). **Methods** A total of 163 patients diagnosed with colorectal cancer between Apr. 2021 and Jan. 2022 were enrolled from Shuguang Hospital of Shanghai University of Traditional Chinese Medicine. They were categorized into 2 groups: non-metastatic group (CRC-NM group, n=82) and CRC-LM group (n=81). Clinical data and peripheral blood samples were collected from all the participants, the quality of life was evaluated using Karnofsky performance status (KPS) score, the levels of total bile acid (TBA) and tumor markers (carcinoembryonic antigen［CEA］ and carbohydrate antigen 125［CA125］) were examined, and the plasma concentrations of 15 BAs were detected using high-performance liquid chromatography/tandem mass spectrometry. The BA concentrations and BA profile were compared between the 2 groups. Additionally, receiver operating characteristic curve was generated to evaluate the efficacy of the BA ratio combined with tumor markers in diagnosing CRC-LM. **Results** No significant difference was found in age, gender, tumor location, degree of pathological differentiation, or KPS score between the 2 groups (all P>0.05). Patients with CRC-LM had significantly higher concentrations of TBA, CEA and CA125 compared to those without metastasis (all P<0.001). Additionally, the concentrations of glycocholic acid, deoxycholic acid, taurodeoxycholic acid, glycodeoxycholic acid, glycoursodeoxycholic acid, lithocholic acid and glycolithocholic acid in patients with CRC-LM were significantly higher compared to patients without metastasis (all P<0.05). Furthermore, the plasma concentration of secondary bile acid (SBA) in CRC-LM patients was significantly higher than that in non-metastatic patients (P<0.001), and the ratio of SBA to primary bile acid (PBA) was also significantly higher in CRC-LM patients (P<0.001). Combination of SBA/PBA ratio with CEA and CA125 yielded a sensitivity of 71.60%, a specificity of 80.49%, and an area under curve of 0.820 (95% confidence interval 0.754 to 0.885, P<0.001). **Conclusion** The plasma BA concentration is elevated in patients with CRC-LM, and the BA profile is notably different from that of patients without metastasis. The SBA/PBA ratio combined with CEA and CA125 demonstrates a great value for diagnosing CRC-LM.

［**Key words**］ colorectal neoplasms; liver metastasis; bile acid; secondary bile acid; diagnostic marker

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结直肠癌是高发病率、高死亡率的消化道恶性肿瘤[1]。近年来，我国结直肠癌发病率呈上升趋势，患者确诊时多为晚期，生存期短、预后差[2]。早中期结直肠癌患者接受手术治疗后仍有1/3发生转移[3]，影响患者的生活质量及预后。肝脏是结直肠癌最常见的转移器官，近一半的结直肠癌患者出现肝转移[4]，及早诊断结直肠癌肝转移对改善患者临床预后非常重要。胆汁酸是胆固醇代谢的重要产物之一，具有维持代谢稳态、调控信号转导等多种生理功能[5]。胆汁酸在结直肠癌发生、发展中扮演重要角色，因其代谢转化依赖多种肝酶，与肝脏功能具有密不可分的联系[6]。目前关于胆汁酸在结直肠癌转移中作用的研究较少，其是否可以用于诊断结直肠癌肝转移尚无明确的临床数据。本研究拟通过比较结直肠癌肝转移与无转移患者的血浆胆汁酸谱特征，筛选肝转移特异性差异胆汁酸并探讨其临床应用价值。

1　资料和方法

1.1　研究对象　纳入2021年4月至2022年1月于上海中医药大学附属曙光医院就诊的结直肠癌肝转移或无转移患者，病理类型均为腺癌。纳入标准：（1）经手术或活检病理明确诊断为结直肠腺癌，未接受抗肿瘤治疗；（2）肝转移灶通过至少1种影像学方法诊断，或具有病理检查诊断结果；（3）临床资料及相关实验室检查结果完整，且患者自愿接受本研究计划内的观察；（4）预计生存时间>3个月。排除标准：（1）合并心、肝、肾、消化或神经系统等严重疾病；（2）合并其他恶性肿瘤病史；（3）合并自身免疫性肝病、酒精或药物等所致肝硬化；（4）妊娠或哺乳期女性；（5）合并精神障碍疾病，或无法配合研究者。本研究获得上海中医药大学附属曙光医院伦理委员会批准（2021-936-11-02），所有入选患者均签署了知情同意书。

1.2　临床资料收集　收集患者人口学资料（性别、年龄）和肿瘤病理资料（发病部位、病理分化程度），并根据Karnofsky功能状态（Karnofsky performance status，KPS）评分标准评估生存质量。

1.3　生化指标及肿瘤标志物检测　采集患者晨起空腹肘静脉血，静置后分离血清，用于实验室生化指标及肿瘤标志物检测。采用Beckman

全自动生化分析仪检测丙氨酸转氨酶（alanine aminotransferase，ALT）、天冬氨酸转氨酶（aspartate aminotransferase，AST）、总胆红素（total bilirubin，TBil）、总蛋白（total protein，TP）、总胆汁酸（total bile acid，TBA）及空腹血糖（fasting blood glucose，FBG）。采用HPLC检测糖化血红蛋白（glycosylated hemoglobin，HbA1c）。采用电化学发光免疫分析法检测癌胚抗原（carcinoembryonic antigen，CEA）及糖类抗原125（carbohydrate antigen 125，CA125）。

1.4　胆汁酸检测　采集患者晨起空腹肘静脉血，静置后分离血浆，样本置于−80 ℃冰箱储存。采用高效液相色谱-串联质谱法检测血浆中15种胆汁酸含量，包括胆酸（cholic acid，CA）、牛磺胆酸（taurocholic acid，TCA）、甘氨胆酸（glycocholic acid，GCA）、鹅脱氧胆酸（chenodeoxycholic acid，CDCA）、牛磺鹅脱氧胆酸（taurochenodeoxycholic acid，TCDCA）、甘氨鹅脱氧胆酸（glycochenodeoxycholic acid，GCDCA）、脱氧胆酸（deoxycholic acid，DCA）、牛磺脱氧胆酸（taurodeoxycholic acid，TDCA）、甘氨脱氧胆酸（glycodeoxycholic acid，GDCA）、熊脱氧胆酸（ursodeoxycholic acid，UDCA）、牛磺熊脱氧胆酸（tauroursodeoxycholic acid，TUDCA）、甘氨熊脱氧胆酸（glycoursodeoxycholic acid，GUDCA）、石胆酸（lithocholic acid，LCA）、牛磺石胆酸（taurolithocholic acid，TLCA）和甘氨石胆酸（glycolithocholic acid，GLCA）。样品分析采用美国SCIEX公司API 3200LC/MS-MS系统。计算初级胆汁酸（primary bile acid，PBA）含量、次级胆汁酸（secondary bile acid，SBA）含量和SBA/PBA比值，其中PBA包括CA、TCA、GCA、CDCA、TCDCA、GCDCA，SBA包括DCA、TDCA、GDCA、UDCA、TUDCA、GUDCA、LCA、TLCA、GLCA。

1.5　统计学处理　采用SPSS 27.0软件及MedCalc 22.018软件进行统计学分析。用Kolmogorov-Smirnov检验对连续变量进行正态性检验，符合正态分布的连续变量以$\bar{x}\pm s$描述，两组间比较采用独立样本t检验；不符合正态分布的连续变量以中位数（下四分位数，上四分位数）描述，两组间比较采用Mann-Whitney U检验。分类变量以例数和百分数描述，两组间比较采用χ^2检验。构建多指标联合诊断的logistic回归模型，绘制ROC曲线评估单个指标及联合诊断模型的诊断价值。检验水准（α）为0.05。

2　结　果

2.1　两组患者一般临床特征比较　共纳入163例结直肠腺癌患者，其中无转移组82例、肝转移组81例。两组患者性别、年龄、肿瘤位置、病理分化程度及KPS评分差异均无统计学意义（均$P>0.05$），见表1。

表1　两组结直肠癌患者一般临床特征

Tab 1　Clinical characteristics of patients with colorectal cancer in 2 groups

n (%)

Index	CRC-NM group $N=82$	CRC-LM group $N=81$
Gender		
Male	54 (65.85)	54 (66.67)
Female	28 (34.15)	27 (33.33)
Age/year		
≤60	28 (34.15)	26 (32.10)
>60	54 (65.85)	55 (67.90)
Tumor location		
Colon	46 (56.10)	42 (51.85)
Rectum	36 (43.90)	39 (48.15)
Pathologic differentiation		
Well	7 (8.54)	9 (11.11)
Moderately	58 (70.73)	54 (66.67)
Poorly	17 (20.73)	18 (22.22)
KPS score		
90-100	36 (43.90)	34 (41.98)
80-<90	46 (56.10)	47 (58.02)

CRC-NM: Colorectal cancer non-metastasis; CRC-LM: Colorectal cancer liver metastasis; KPS: Karnofsky performance status.

2.2　两组患者生化指标及肿瘤标志物比较　两组结直肠癌患者ALT、AST、TBil、TP、FBG、HbA1c水平差异无统计学意义（均$P>0.05$）。肝转移组患者TBA、CEA、CA125较无转移组患者升高，差异有统计学意义（均$P<0.001$）。见表2。

2.3　两组患者血浆15种胆汁酸含量比较　两组结直肠癌患者CA、TCA、CDCA、TCDCA、GCDCA、UDCA、TUDCA、TLCA含量差异无统计学意义（均$P>0.05$）。肝转移组患者GCA、DCA、TDCA、GDCA、GUDCA、LCA及GLCA含量较无转移组患者升高，差异有统计学意义（均$P<0.05$）。见表3。

表2　两组结直肠癌患者生化指标及肿瘤标志物比较

Tab 2　Comparison of clinical data and tumor markers of patients with colorectal cancer between 2 groups

Index	CRC-NM group n=82	CRC-LM group n=81	Statistic	P value
ALT/(U•L^{-1}), M (Q_L, Q_U)	19.00 (14.00, 30.00)	18.00 (12.00, 29.00)	U=3 153.50	0.578
AST/(U•L^{-1}), M (Q_L, Q_U)	21.00 (17.00, 28.00)	23.00 (17.00,29.00)	U=3 180.50	0.640
TBil/(μmol•L^{-1}), M (Q_L, Q_U)	14.60 (11.90, 19.00)	13.20 (10.90, 18.50)	U=2 991.50	0.274
TP/(g•L^{-1}), $\bar{x}\pm s$	70.05±6.37	78.72±6.47	t=1.32	0.188
FBG/(mmol•L^{-1}), M (Q_L, Q_U)	4.90 (4.50, 5.58)	5.00 (4.80, 5.90)	U=2 858.00	0.124
HbA1c/%, M (Q_L, Q_U)	5.60 (5.30, 6.10)	5.60 (5.30, 6.30)	U=3 311.50	0.975
TBA/(μmol•L^{-1}), M (Q_L, Q_U)	3.72 (2.34, 4.57)	5.24 (2.33, 8.82)	U=2 324.00	<0.001
CEA/(μg•mL^{-1}), M (Q_L, Q_U)	3.37 (2.27, 6.46)	10.91 (3.23, 23.21)	U=1 776.00	<0.001
CA125/(U•mL^{-1}), M (Q_L, Q_U)	9.70 (6.91, 16.00)	22.20 (8.90, 42.70)	U=2 056.50	<0.001

CRC-NM: Colorectal cancer non-metastasis; CRC-LM: Colorectal cancer liver metastasis; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TBil: Total bilirubin; TP: Total protein; FBG: Fasting blood glucose; HbA1c: Glycosylated hemoglobin; TBA: Total bile acid; CEA: Carcinoembryonic antigen; CA125: Carbohydrate antigen 125; M (Q_L, Q_U): Median (lower quartile, upper quartile).

表3　两组结直肠癌患者15种血浆胆汁酸含量及胆汁酸谱分布比较

Tab 3　Comparison of concentrations of 15 plasma bile acids and bile acid profile of patients with colorectal cancer between 2 groups

M (Q_L, Q_U)

Index	CRC-NM group n=82	CRC-LM group n=81	U value	P value
CA/(nmol•L^{-1})	165.50 (55.50, 281.00)	173.00 (64.08, 305.00)	3 248.00	0.809
TCA/(nmol•L^{-1})	11.40 (8.02, 24.45)	17.90 (9.83, 60.60)	2 757.00	0.061
GCA/(nmol•L^{-1})	208.24 (98.82, 298.00)	402.83 (170.00, 498.00)	1 985.00	<0.001
CDCA/(nmol•L^{-1})	859.50 (348.00, 1 360.00)	527.00 (245.00, 922.00)	2 764.50	0.065
TCDCA/(nmol•L^{-1})	85.10 (36.70, 163.00)	88.16 (28.10, 199.00)	3 094.00	0.451
GCDCA/(nmol•L^{-1})	832.50 (453.00, 1 502.50)	989.43 (327.00, 2 920.00)	3 014.00	0.308
DCA/(nmol•L^{-1})	166.00 (8.86, 565.00)	535.00 (278.00, 1 002.50)	2 112.50	<0.001
TDCA/(nmol•L^{-1})	11.30 (0.26, 43.38)	31.00 (7.50, 100.00)	2 129.50	<0.001
GDCA/(nmol•L^{-1})	82.85 (2.90, 237.62)	292.02 (107.00, 842.00)	1 947.00	<0.001
UDCA/(nmol•L^{-1})	131.43 (41.00, 195.50)	109.00 (47.40, 348.36)	2 893.00	0.155
TUDCA/(nmol•L^{-1})	4.01 (2.10, 5.45)	6.56 (1.23, 11.10)	2 836.00	0.107
GUDCA/(nmol•L^{-1})	89.46 (37.19, 270.00)	104.00 (41.80, 953.00)	2 671.00	0.031
LCA/(nmol•L^{-1})	14.60 (8.39, 22.53)	27.60 (10.50, 53.75)	2 327.00	<0.001
TLCA/(nmol•L^{-1})	0.78 (0.20, 2.40)	1.06 (0.16, 3.01)	2 952.50	0.221
GLCA/(nmol•L^{-1})	3.80 (1.68, 15.44)	13.10 (3.01, 42.14)	2 509.50	0.007
PBA/(nmol•L^{-1})	2 782.46 (1 520.90, 3 625.40)	2 956.10 (1 442.65, 4 679.62)	2 987.00	0.268
SBA/(nmol•L^{-1})	812.41 (339.96, 1 477.01)	1 820.82 (870.33, 3 209.81)	1 742.00	<0.001
SBA/PBA ratio	0.37 (0.17, 0.58)	0.96 (0.44, 1.43)	1 801.00	<0.001

CRC-NM: Colorectal cancer non-metastasis; CRC-LM: Colorectal cancer liver metastasis; CA: Cholic acid; TCA: Taurocholic acid; GCA: Glycocholic acid; CDCA: Chenodeoxycholic acid; TCDCA: Taurochenodeoxycholic acid; GCDCA: Glycochenodeoxycholic acid; DCA: Deoxycholic acid; TDCA: Taurodeoxycholic acid; GDCA: Glycodeoxycholic acid; UDCA: Ursodeoxycholic acid; TUDCA: Tauroursodeoxycholic acid; GUDCA: Glycoursodeoxycholic acid; LCA: Lithocholic acid; TLCA: Taurolithocholic acid; GLCA: Glycolithocholic acid; PBA: Primary bile acid; SBA: Secondary bile acid; M (Q_L, Q_U): Median (lower quartile, upper quartile).

2.4　两组患者血浆PBA含量、SBA含量和SBA/PBA比值比较　两组结直肠癌患者血浆PBA含量差异无统计学意义（P>0.05）。肝转移组患者血浆SBA含量和SBA/PBA比值高于无转移组患者，

差异有统计学意义（均 $P<0.001$）。见表 3。

2.5　SBA/PBA 比值联合 CEA、CA125 对结直肠癌肝转移的诊断价值　ROC 曲线分析（图 1）显示，CEA 单独诊断结直肠癌肝转移的灵敏度为 66.67%、特异度为 68.29%、AUC 为 0.733（95% *CI* 0.657～0.809），CA125 单独诊断结直肠癌肝转移的灵敏度为 51.85%、特异度为 84.15%、AUC 为 0.690（95% *CI* 0.609～0.772），SBA/PBA 比值单独诊断结直肠癌肝转移的灵敏度为 55.56%、特异度为 90.24%、AUC 为 0.729（95% *CI* 0.649～0.809）。CEA＋CA125＋SBA/PBA 比值联合诊断结直肠癌肝转移的灵敏度为 71.60%，优于 CEA、CA125、SBA/PBA 比值单项指标；特异度为 80.49%，优于 CEA 单项指标；AUC 为 0.820（95% *CI* 0.754～0.885），优于 CEA（$P=0.017$）、CA125（$P=0.003$）及 SBA/PBA 比值（$P=0.001$）单项指标。

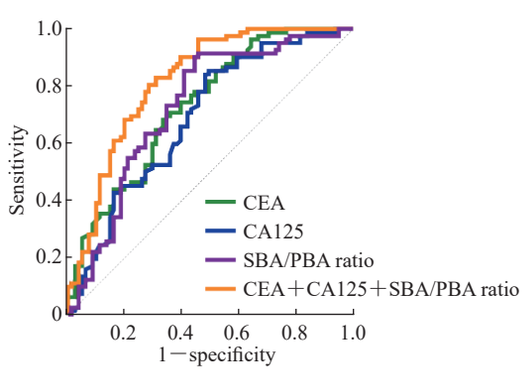

图 1　CEA、CA125、SBA/PBA 比值单独及联合检测诊断结直肠癌肝转移的 ROC 曲线分析

Fig 1　ROC curves of CEA, CA125 and SBA/PBA ratio and their combination for detection of colorectal cancer liver metastasis

CEA: Carcinoembryonic antigen; CA125: Carbohydrate antigen 125; SBA: Secondary bile acid; PBA: Primary bile acid; ROC: Receiver operating characteristic.

3　讨　论

胆汁酸是胆固醇的主要代谢产物之一，胆固醇在肝脏中分解形成 PBA，进一步与牛磺酸或甘氨酸结合形成结合型 PBA，随胆汁进入肠道。结合型 PBA 在多种肠道菌群的作用下，通过脱羟基、脱氢、差向异构化等次级转化过程生成 SBA[6]。生理浓度的胆汁酸积极参与人体脂质、脂溶性维生素的代谢吸收过程，而比例失调的胆汁酸通过引起细胞 DNA 损伤、诱导慢性炎症反应、激活癌症通路、参与调节宿主免疫及代谢表型等多种途径影响结直肠癌的发生、发展[7]。多项临床研究显示，与健康志愿者比较，结直肠癌患者血浆或粪便胆汁酸总量升高且胆汁酸谱分布异常，提示其可作为肠癌风险预测的临床指标之一[8-9]。

本研究发现在肝功能及糖代谢功能相似的情况下，结直肠癌肝转移患者血清 TBA 含量高于无转移患者（$P<0.001$），并且肝转移组患者血浆 GCA、DCA、TDCA、GDCA、GUDCA、LCA 及 GLCA 含量高于无转移患者（均 $P<0.05$）。一项前瞻性研究筛选出 GCA、TCA、GCDCA、TCDCA、甘氨猪胆酸、GDCA 及 TDCA 共 7 种血浆胆汁酸，发现其升高与结肠癌风险呈正相关[10]。另一项临床队列显示，有高结直肠癌患病风险的人群粪便中 DCA 浓度高于健康对照人群[11]。TDCA 的增多同样被认为与结直肠癌风险密切相关，而激活 MAPK/ERK 信号通路、破坏肠屏障功能可能是 TDCA 促进结直肠癌进展的机制之一[12]。本研究结果补充了促肿瘤作用胆汁酸与结直肠癌转移有关的临床证据。

PBA 在肝脏中的合成受到长期高脂、高蛋白、低纤维饮食的影响，这也是公认的结直肠癌发生的重要危险因素。除此之外，PBA 进入肠道经过肠道菌群直接或间接的修饰转化后产生大量 SBA。研究显示，超生理剂量的 SBA 可激活多条肿瘤相关信号通路，促进肿瘤发生[13-14]。同时，SBA 还可激活 Wnt/β- 联蛋白信号通路[15]，参与肿瘤血管新生[16]，促进结肠癌转移。本研究在结直肠癌肝转移患者血浆中筛选出升高的 7 种胆汁酸，其中 6 种为 SBA，进一步分析发现肝转移患者血浆 SBA 含量和 SBA/PBA 比值较无转移患者明显升高（$P<0.001$）。

CEA 与 CA125 是临床应用广泛的肿瘤标志物，在消化道肿瘤尤其是结直肠癌的临床诊断与预后预测中具有较高临床价值。本研究评估了 CEA 与 CA125 在结直肠癌肝转移临床诊断中的价值，与既往研究结果[17]相似。血清肿瘤标志物及多种指标的联合检测有助于提高结直肠癌的诊断效能[18]。多项研究提示了胆汁酸在肿瘤疾病中的临床诊断价值[19-20]。Costarelli 等[21]发现，DCA/CA 比值与结直肠癌发生风险呈正相关，并证实了胆汁酸比值在疾病流行病学研究的可重复性与临床价值。本研

究结果提示SBA/PBA比值与CEA、CA125联合检测对结直肠癌肝转移有较好的诊断效能，灵敏度为71.60%、特异度为80.49%、AUC为0.820，且优于单项指标。这提示胆汁酸与肿瘤标志物联合诊断结直肠癌肝转移具有临床应用潜力，但其可重复性与稳定性还需要更大样本量的临床队列及更完善的研究设计验证。

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