

· 肝脏肿瘤 ·

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血浆胆汁酸在肝肿瘤中的差异分析及应用价值

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摘要: **目的** 分析原发性肝癌与转移性肝癌患者血浆胆汁酸水平及其与临床指标的相关性,并评估其联合 AFP 对于原发性肝癌的诊断价值。**方法** 纳入 2020 年 8 月—2021 年 9 月于上海中医药大学附属曙光医院就诊且具有组织病理学及影像学明确的 75 例原发性肝癌患者及 79 例转移性肝癌患者,采集外周血并分别分离血清及血浆,比色法及色谱法检测生化指标,电化学发光免疫分析法检测肿瘤标志物水平,高效液相色谱-串联质谱法检测胆汁酸含量。符合正态分布的计量资料两组间比较采用成组 *t* 检验,不符合正态分布的计量资料两组间比较采用 Mann-Whitney *U* 检验。相关性检验采用 Spearman 相关分析。临床诊断效能采用受试者工作特征曲线(ROC 曲线)评估。**结果** 原发性肝癌组患者 TC、TG、LDL-C 及载脂蛋白(Apo)B 显著低于转移性肝癌组患者,差异均具有统计学意义(*U* 值分别为 1 598、1 255、909、889, *P* 值均 < 0.05)。原发性肝癌组患者 AFP 显著高于转移性肝癌组患者,癌胚抗原(CEA)显著低于转移性肝癌组患者,差异均具有统计学意义(*U* 值分别为 1 873、926, *P* 值均 < 0.05)。原发性肝癌组患者总胆汁酸(TBA)、胆酸(CA)、鹅脱氧胆酸(CDCA)、熊脱氧胆酸(UDCA)、牛磺胆酸(TCA)、牛磺鹅脱氧胆酸(TCDCA)、甘氨酸(GCA)、甘氨酸鹅脱氧胆酸(GCDCA)、牛磺熊脱氧胆酸(TUDCA)、甘氨酸熊脱氧胆酸(GUDCA)均显著高于转移性肝癌患者,脱氧胆酸(DCA)显著低于转移性肝癌患者,差异均具有统计学意义(*P* 值均 < 0.05)。总人群中 TBA、CDCA、GCA、GCDCA、GUDCA、TCA、TCDCA 及 TUDCA 含量与 AFP 水平呈显著正相关(*P* 值均 < 0.05)。原发性肝癌患者中 GCA、TCA、TCDCA 及 TUDCA 含量与 AFP 水平呈显著正相关(*P* 值均 < 0.05)。AFP+TCA+GCA+TCDCA 联合检测的 AUC 为 0.822(95%CI: 0.746 ~ 0.898, *P* < 0.000 1),效能最高。**结论** 原发性肝癌与转移性肝癌患者血浆胆汁酸含量具有显著差异,差异性胆汁酸与肝损伤及 AFP 升高密切相关,联合 AFP 对原发性肝癌具有更优的临床诊断价值。

关键词: 胆汁酸类和盐类; 肝肿瘤; 肿瘤转移**基金项目:** 国家自然科学基金(82104619); 上海市卫健委卫生行业临床研究专项(20214Y0455); 上海中医药大学预算内项目(2021LK105)

Differences and application value of plasma bile acids in tumors of the liver

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Abstract: Objective To investigate the levels of plasma bile acids (BA) in patients with primary liver cancer (PLC) or metastatic liver cancer (MLC) and their correlation with clinical indicators, as well as the value of plasma BAs combined with alpha-fetoprotein (AFP) in the diagnosis of PLC. **Methods** This study was conducted among 75 patients with PLC and 79 patients

with MLC who attended Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine from August 2020 to September 2021 and had a confirmed diagnosis based on histopathological and imaging findings. Peripheral blood samples were collected from all patients, and serum and plasma were separated. Colorimetry and chromatography were used to measure biochemical parameters; electrochemiluminescence immunoassay was used to measure the levels of tumor markers; liquid chromatography-tandem mass spectrometry was used to measure the content of BA. The *t*-test was used for comparison of normally distributed continuous data, and the Mann-Whitney *U* test was used for comparison of non-normally distributed continuous data; the Spearman's coefficient was used for correlation analysis; the receiver operating characteristic (ROC) curve was used to evaluate clinical diagnostic efficacy. **Results** The PLC group had significantly lower levels of total cholesterol, triglyceride, low-density lipoprotein cholesterol, and apolipoprotein B than the MLC group ($U=1\ 598, 1\ 255, 909, \text{ and } 889$, all $P<0.05$). Compared with the MLC group, the PLC group had a significantly higher level of AFP and a significantly lower level of carcinoembryonic antigen ($U=1\ 873$ and 926 , both $P<0.05$). Compared with the MLC group, the PLC group had significantly higher levels of TBA, CA, CDCA, UDCA, TCA, TCDCA, GCA, GCDCA, TUDCA, and GUDCA and a significantly lower level of DCA (all $P<0.05$). In the total population, the levels of TBA, CDCA, GCA, GCDCA, GUDCA, TCA, TCDCA, and TUDCA were significantly positively correlated with the level of AFP (all $P<0.05$). In the patients with PLC, the levels of GCA, TCA, TCDCA, and TUDCA were significantly positively correlated with the level of AFP (all $P<0.05$). Combined measurement of AFP+TCA+GCA+TCDCA had an area under the ROC curve of 0.822 (95% confidence interval: 0.746—0.898, $P<0.000\ 1$), suggesting that it had the highest diagnostic efficacy. **Conclusion** There are significant differences in the levels of plasma BA between the patients with PLC and those with MLC, and the differentially expressed BAs are closely associated with liver function impairment and the increase in AFP. BAs combined with AFP has a better clinical value in the diagnosis of PLC.

Key words: Bile Acids and Salts; Liver Neoplasms; Neoplasm Metastasis

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胆汁酸是胆固醇分解代谢的主要产物,研究^[1]显示胆汁酸在维持生理功能、代谢稳态等多方面发挥作用,其代谢分布异常与糖尿病^[2]、非酒精性脂肪性肝病^[3]、阿尔兹海默病^[4]及消化道肿瘤^[5]等多种疾病的发生发展密切相关。胆固醇在肝脏中通过经典途径和替代途径分别分解代谢生成初级胆汁酸,随胆汁进入肠道,在菌群作用下经生物转化生成次级胆汁酸,大部分胆汁酸在位于回肠的胆汁酸转运体的作用下重吸收,形成“肝-肠循环”。研究^[6-7]显示初级和次级胆汁酸可以多途径地影响肝癌病程。同时,临床研究显示胆汁酸在健康人群中具有鉴别肝癌的能力,且在鉴别肝癌与肝硬化^[8]、非酒精性脂肪性肝炎^[9]、病毒性肝炎^[10]等其他肝脏疾病中具有一定的临床价值。同时,胆汁酸还在肝癌疾病进程中具有预测价值^[8]。转移性肝癌是发生在肝脏的继发性肿瘤病灶,肝脏是大肠癌、胃癌、胰腺癌、乳腺癌等多种肿瘤最常见的转移部位,也常是多发转移部位的晚期肿瘤患者最先诊断的病灶^[11],当原发灶发病隐匿或受解剖位置影响不便活检时,对原发性肝癌与转移性肝癌的鉴别是临床诊疗过程中的关键环节。目前,胆汁酸代谢在原发性肝癌与转移性肝癌之间是否有差异,其异常

代谢是否可以对两者有效区分,尚缺乏临床数据。因此,本研究以原发性肝癌及转移性肝癌患者为研究对象,分析两组患者的血浆胆汁酸谱特征,筛选差异性代谢物并探讨其临床意义。

1 资料与方法

1.1 研究对象 选取2020年8月—2021年9月于上海中医药大学附属曙光医院就诊且具有病理组织学及影像学明确的原发性肝癌患者及转移性肝癌患者。原发性肝癌患者属于原发性肝癌组,大肠癌肝转移患者属于转移性肝癌组。纳入标准:(1)原发灶通过病理组织学确诊为肝癌或大肠癌;(2)转移灶通过至少一个影像学诊断,或具有病理检查诊断;(3)Karnofsky功能状态(Karnofsky performance status)评分 ≥ 80 分,预计生存期均 >3 个月。排除标准:(1)合并HAV、HCV等嗜肝病毒感染或自身免疫、酒精、药物等肝硬化患者;(2)合并溃疡型性肠炎、免疫性肠炎及其他自身免疫疾病患者;(3)既往有除原发性肝癌及转移性肝癌以外的其他恶性肿瘤病史或合并其他恶性肿瘤患者;(4)妊娠或哺乳期女

性;(5)合并不易控制的精神类疾病,无法配合收集病史及样本采集,或临床资料不全者。

1.2 研究方法

1.2.1 样本采集 嘱采集对象20:00后禁食禁水,第二天采集晨起空腹肘静脉血,分离血清及血浆,用于临床生化指标、肿瘤标志物及胆汁酸检测。处理后样本于-80℃冰箱冻存。

1.2.2 生化指标检测 ALT、AST、TBil、血糖(GLU)、TC、TG、HDL-C、LDL-C、载脂蛋白(Apo)A1及ApoB采用Beckman全自动生化分析仪检测。糖化血红蛋白(glycosylated hemoglobin type A1c, HbA1c)采用高压液相色谱法检测。

1.2.3 肿瘤标志物检测 AFP、癌胚抗原(CEA)、糖类抗原(CA)19-9及CA125采用电化学发光免疫分析法检测,购自罗氏及雅培公司。

1.2.4 胆汁酸检测 总胆汁酸(total bile acid, TBA)、胆酸(cholic acid, CA)、鹅脱氧胆酸(chenodeoxycholic acid, CDCA)、脱氧胆酸(deoxycholic acid, DCA)、熊脱氧胆酸(ursodeoxycholic acid, UDCA)、石胆酸(lithocholic acid, LCA)、牛磺胆酸(taurocholic acid, TCA)、牛磺鹅脱氧胆酸(taurochenodeoxycholic acid, TCDCA)、甘氨酸胆酸(glycocholic acid, GCA)、甘氨酸鹅脱氧胆酸(glycochenodeoxycholic acid, GCDCA)、牛磺脱氧胆酸(taurodeoxycholic acid, TDCA)、牛磺熊脱氧胆酸(tauroursodeoxycholic acid, TUDCA)、牛磺石胆酸(tauroolithocholic acid, TLCA)、甘氨酸脱氧胆酸(glycodeoxycholic acid, GDCA)、甘氨酸熊脱氧胆酸(glycoursodeoxycholic acid, GUDCA)及甘氨酸石胆酸(glycolithocholic acid, GLCA)采用高效液相色谱-串联质谱法检测,购自SCIEX公司。

1.3 统计学方法 采用SPSS 27.0、MedCalc 22.018软件进行统计学分析,采用GraphPad Prism 9.5.1软件绘图。正态性检验采用Kolmogorov-Smirnov *t* 检验,计量资料符合正态分布采用 $\bar{x}\pm s$ 表示,两组间比较采用成组*t* 检验;不符合正态分布以 $M(P_{25}\sim P_{75})$ 表示,两组间比较采用Mann-Whitney *U* 检验。评估两变量的相关系数采用Spearman相关性检验。指标诊断分析采用受试者工作特征曲线(ROC曲线)绘制。*P*<0.05为差异有统计学意义。

2 结果

2.1 两组患者一般情况比较 本研究共纳入154例患者。原发性肝癌组共纳入75例,其中男54例,女21例;平均年龄65.93岁,年龄范围31~85岁;肝细胞癌61例,胆管细胞癌14例;CNLC分期Ⅱ期30例,Ⅲ期45例。转移性肝癌组共纳入79例,其中男53例,女26例;平均年龄61.48岁,年龄范围30~82岁;结肠癌48例,直肠癌31例,病理类型均为腺癌;TNM分期均为Ⅳ期。

2.2 两组患者生化指标水平比较 选取指标包括肝功能、糖代谢及脂代谢相关指标。两组患者ALT、AST、TBil、GLU、HbA1c、HDL-C及ApoA1组间比较差异均无统计学意义(*P*值均>0.05),转移性肝癌患者的TC、TG、LDL-C及ApoB较原发性肝癌患者显著升高(*P*值均<0.05)(表1)。

2.3 两组患者肿瘤标志物水平比较 选取指标以消化道肿瘤相关指标为主。原发性肝癌患者AFP水平显著高于转移性肝癌患者(*P*<0.05),转移性肝癌患者CEA水平显著高于原发性肝癌患者(*P*<0.05),两组间在CA19-9、CA125比较时差异无统计学意义(*P*值均>0.05)(表2)。

表1 两组患者生化指标比较

Table 1 Comparison of levels of laboratory tests between patients with primary liver cancer or metastatic liver cancer

项目	原发性肝癌组(<i>n</i> =75)	转移性肝癌组(<i>n</i> =79)	统计值	<i>P</i> 值
ALT(U/L)	25.00(18.00~33.00)	22.00(12.00~37.00)	<i>U</i> =2 375	0.177
AST(U/L)	31.00(27.25~52.00)	29.00(20.75~46.00)	<i>U</i> =1 933	0.063
TBil(μmol/L)	20.10(13.70~30.90)	15.85(12.63~28.80)	<i>U</i> =2 407	0.059
GLU(mmol/L)	5.30(4.60~6.00)	5.05(4.70~6.00)	<i>U</i> =2 636	0.925
HbA1c(%)	5.40(4.90~6.00)	5.50(5.10~6.00)	<i>U</i> =2 140	0.205
TC(mmol/L)	3.87(3.31~4.58)	4.81(4.18~5.91)	<i>U</i> =1 598	<0.001
TG(mmol/L)	1.04(0.88~1.38)	1.31(1.07~1.85)	<i>U</i> =1 255	<0.001
HDL-C(mmol/L)	1.07±0.29	1.09±0.34	<i>t</i> =0.243	0.867
LDL-C(mmol/L)	2.09(1.45~2.73)	3.06(2.38~4.08)	<i>U</i> =909	<0.001
ApoA1(g/L)	0.90(0.73~1.06)	0.93(0.81~1.14)	<i>U</i> =1 474	0.154
ApoB(g/L)	0.67(0.49~0.89)	0.93(0.69~1.16)	<i>U</i> =889	<0.001

2.4 两组患者血浆胆汁酸含量比较 共检测血浆中15种胆汁酸含量。原发性肝癌患者血浆TBA含量显著高于转移性肝癌患者($P<0.05$)。比较两组患者结合型胆汁酸含量,原发性肝癌患者TCA、TCDCA、GCA、GCDCA、TUDCA、GUDCA显著高于转移性肝癌患者(P 值均 <0.05)。在游离型胆汁酸中,原发性肝癌患者CA、CDCA、UDCA显著高于转移性肝癌患者(P 值均 <0.05),而DCA显著低于转移性肝癌患者($P<0.05$)。两组间在LCA、TDCA、TLCA、GDCA、GLCA含量比较时差异均无统计学意义(P 值均 >0.05)(表3)。

2.5 差异性胆汁酸的临床相关性分析 以2.4节中发现的两组间差异胆汁酸为研究对象。在总人群中,患者血浆TBA、GCA、GCDCA、TCA、TCDCA及TUDCA含量与ALT、AST及TBil水平呈显著正相关(P 值均 <0.05),CDCA、UDCA及GUDCA含量与TBil水平呈显著正相关(P 值均 <0.05);TBA、CDCA、GCA、GCDCA、GUDCA、TCA、TCDCA及TUDCA含量与AFP水平呈显著正相关(P 值均 <0.05),DCA含量与AFP水平呈显著负相关($P<0.05$),TBA、CDCA、UDCA及GUDCA含量与CEA水平呈

显著负相关(P 值均 <0.05)(图1)。在原发性肝癌患者人群中,患者血浆TBA、GCA、TCA及TCDCA含量与AST及TBil水平呈显著正相关(P 值均 <0.05),GCDCA含量与AST水平呈显著正相关($P<0.05$),UDCA、GUDCA及TUDCA含量与TBil水平呈显著正相关(P 值均 <0.05);GCA、TCA、TCDCA及TUDCA含量与AFP水平呈显著正相关(P 值均 <0.05);DCA含量与TBil水平呈显著负相关($P<0.05$)(图2)。

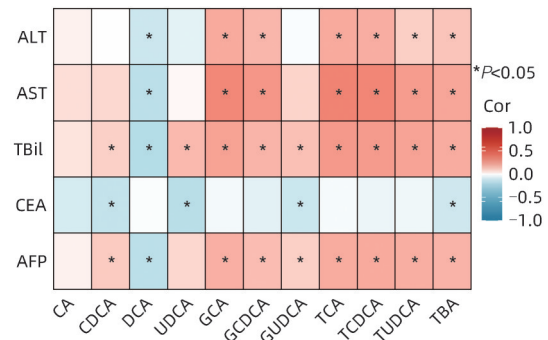


图1 总人群中血浆胆汁酸含量与临床指标的相关性分析
Figure 1 Correlation analysis of plasma BA and clinical markers in all liver cancer patients

表2 两组患者肿瘤标志物水平比较

Table 2 Comparison of levels of serum tumor markers between patients with primary liver cancer or metastatic liver cancer

项目	原发性肝癌组(n=75)	转移性肝癌组(n=79)	U值	P值
AFP(ng/mL)	6.45(3.16~15.74)	4.02(2.54~5.23)	1 873	<0.001
CEA(ng/mL)	3.04(2.53~5.42)	15.14(5.02~83.18)	926	<0.001
CA19-9(U/mL)	21.20(10.83~54.69)	21.36(10.22~154.38)	2 361	0.840
CA125(U/mL)	18.70(12.50~36.20)	21.20(10.55~44.63)	1 181	0.128

表3 两组患者血浆胆汁酸含量比较

Table 3 Comparison of concentrations of plasma BA between patients with primary liver cancer or metastatic liver cancer

项目	原发性肝癌组(n=75)	转移性肝癌组(n=79)	U值	P值
TBA(nmol/L)	11 675.7(6 098.5~33 679.9)	5 241.6(2 445.8~10 062.8)	886	<0.001
CA(nmol/L)	290.7(148.6~1 030.0)	114.0(62.8~319.0)	1 084	<0.001
CDCA(nmol/L)	2 570.0(766.4~3 040.0)	527.0(191.5~1 127.2)	750	<0.001
DCA(nmol/L)	66.9(6.9~354.0)	238.3(19.1~572.0)	1 223	0.010
UDCA(nmol/L)	199.0(109.5~572.5)	68.7(26.8~246.5)	1 039	<0.001
LCA(nmol/L)	15.7(6.3~45.6)	21.2(10.7~39.9)	1 476	0.243
TCA(nmol/L)	444.0(90.3~2 231.1)	47.2(11.3~482.2)	862	<0.001
TCDCA(nmol/L)	627.0(256.0~5 060.0)	145.0(48.7~981.9)	828	<0.001
GCA(nmol/L)	1 309.2(424.0~4 670.0)	444.6(190.5~1 400.4)	1 018	<0.001
GCDCA(nmol/L)	3 530.0(1 160.0~13 341.0)	1 149.3(388.4~3 537.4)	978	<0.001
TDCA(nmol/L)	23.6(0.0~114.0)	25.6(5.0~92.3)	1 423	0.144
TUDCA(nmol/L)	41.8(10.8~117.0)	7.3(1.9~21.5)	832	<0.001
TLCA(nmol/L)	0.9(0.2~4.0)	0.9(0.0~2.3)	1 520	0.352
GDCA(nmol/L)	119.8(5.9~609.0)	187.0(13.7~498.0)	1 586	0.570
GUDCA(nmol/L)	434.0(156.8~1 390.0)	104.0(49.9~637.1)	986	<0.001
GLCA(nmol/L)	5.2(0.6~29.0)	6.4(1.8~19.8)	1 641	0.789

2.6 AFP联合血浆胆汁酸区分原发性肝癌的临床价值
选取2.5节中与临床指标显著相关的血浆胆汁酸,联合AFP构建Logistic回归模型,并采用ROC曲线分析单项及联合指标对原发性肝癌的区分能力。结果显示AFP单项指标的ROC曲线下面积(AUC)为0.680(95%CI:0.593~0.767, $P=0.0001$), AFP+TBA联合检测的AUC为0.783(95%CI: 0.694~0.874, $P<0.0001$), AFP+TCA+GCA+TCDCA联合检测的AUC为0.822(95%CI:0.746~0.898, $P<0.0001$),区分效能优于AFP单项指标(图3)。

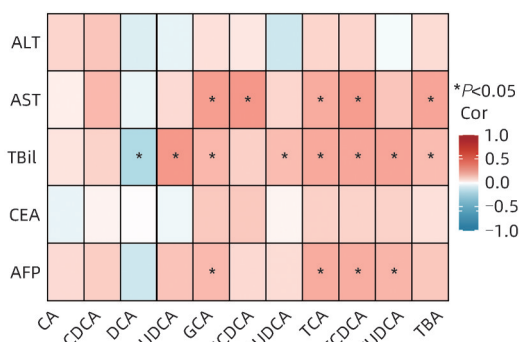


图2 原发性肝癌人群中血浆胆汁酸含量与临床指标的相关性分析

Figure 2 Correlation analysis of plasma BA and clinical markers in primary liver cancer patients

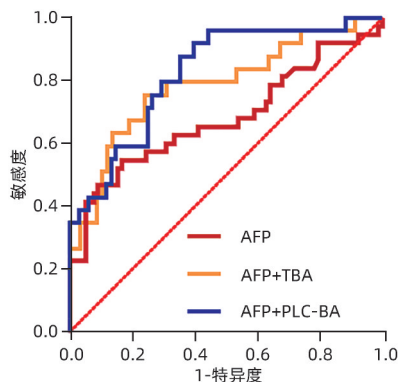


图3 AFP联合血浆胆汁酸区别原发性肝癌的ROC曲线分析
Figure 3 ROC curves of AFP combined with plasma BA for detection of primary liver cancer

3 讨论

胆汁酸的合成和排泄是脂肪和胆固醇代谢的主要途径,其代谢异常与肥胖、糖尿病、非酒精性脂肪性肝病等多种代谢性疾病密切相关^[12]。同时,胆汁酸还可作为信号分子,与多种组织中的多种受体结合,进而激活下游信号通路,发挥生理功能^[13]。近年来,越来越多研究关注到了胆汁酸的异常代谢与恶性肿瘤的密切关系。研究提示,胆汁酸通过诱导细胞凋亡^[14]、介导肿瘤免

疫^[15]、激活相关信号通路^[16]、调控肿瘤微环境^[17]等多途径影响肝肿瘤的发生发展。肝细胞癌患者血浆胆汁酸的含量及组成与健康志愿者及肝硬化等疾病均存在差异,且具有临床诊断潜力^[18-19]。但原发性肝癌与转移性肝癌的胆汁酸差异及区分效能的相关研究目前较少,拟通过本研究提供一定临床证据支持。

本研究首先比较了两组患者的生化指标,两组患者在肝功能(ALT、AST、TBil)及糖代谢(GLU、HbA1c)相关指标上差异均无统计学意义,提示两组患者一般情况相似。在脂代谢相关指标中,转移性肝癌组患者TC、TG与LDL-C较原发性肝癌组显著升高,这可能与两类疾病的常见诱因相关。目前认为,在我国HBV感染、黄曲霉毒素摄入等仍是原发性肝癌发生的重要原因^[20]。在病毒性肝炎感染方面,与发达国家肝癌患者血清中抗HCV高流行率不同,HCV感染不是我国肝癌发生的主要原因^[21]。而大肠癌的发病与地区经济、饮食习惯、生活方式和环境因素等密切相关,其中高脂、低纤维饮食习惯是重要的危险因素^[22]。另外,肝脏作为大肠癌最容易发生远处转移且通常是唯一受累的靶器官,脂肪肝增加了肝转移的发生及进展风险^[23]。

在肿瘤标志物的比较中,原发性肝癌组AFP显著高于转移性肝癌组,AFP是诊断原发性肝癌的特异性标志物。而转移性肝癌组CEA显著高于原发性肝癌组,CEA是肠癌诊断时敏感度与特异度较好的一项肿瘤标志物。两组CA19-9、CA125指标差异均无统计学意义。

在本项研究中,发现与转移性肝癌患者相比,原发性肝癌患者血浆胆汁酸含量及组分发生了明显的变化。肝脏代谢及肠道菌群的生物修饰是胆汁酸代谢合成的两大途径,两者对机体胆汁酸谱的构成具有同样重要的影响,原发性肝癌与肠癌肝转移患者的肝脏环境及肠道微生态环境的巨大差异,可能是他们TBA含量明显差异的主要原因。原发性肝癌患者血浆TBA、CA、CDCA、UDCA、TCA、TCDCA、GCA、GCDCA、TUDCA、GUDCA均显著高于转移性肝癌患者(P 值均 <0.05)。Luo等^[19]发现肝细胞癌患者血浆GCA、TCA、TCDCA、TDCA均较健康组显著升高,Xiao等^[24]发现肝癌患者血浆GCA、GDCA、GCDCA均高于健康对照组,支持本研究的结果。同时,相较于转移性肝癌组,原发性肝癌组患者血浆DCA显著降低($P<0.05$),这可能与本研究中转移性肝癌原发灶均为大肠癌密切相关。研究提示大肠癌血浆及粪便DCA水平显著升高^[25],高脂饮食诱导的肠道DCA升高促进大肠癌发生发展^[26]。相较于原发性肝癌组,在转移性肝癌组也

观察到了血脂代谢的异常,提示肠癌肝转移的发生与血脂代谢异常及血浆DCA升高三者之间的密切联系。

进一步的相关性分析显示,上述筛选的差异性胆酸与肝功能异常呈正相关($P<0.05$),胆汁酸的生成依赖肝脏的生理功能,肝损伤与胆汁酸代谢异常是相互促进的循环过程。在总人群中与原发性肝癌人群中观察到了异常的胆汁酸与AFP的升高呈显著正相关,提示胆汁酸异常代谢与肿瘤疾病进程密切相关。Chen等^[27]提出血浆GCA、GCDCA含量与肝癌病情进展密切相关,在肝癌病程进展评估上具有较好的潜力。单独应用AFP对原发性肝癌及转移性肝癌进行区分时,AFP的AUC为0.680(95%CI:0.593~0.767, $P=0.0001$),提示AFP可以较好地对两者进行区分。使用TBA与AFP联合时,AFP+TBA的AUC为0.783(95%CI:0.694~0.874, $P<0.0001$)。采用上述差异性胆酸联合分析时,AFP+TCA+GCA+TCDCA联合检测的AUC为0.822(95%CI:0.746~0.898, $P<0.0001$),提示血浆胆汁酸联合AFP可以提高对原发性肝癌与转移性肝癌的区分效能,具有一定的临床应用潜力。除了肝脏代谢外,肠道菌群的生物修饰在胆汁酸的合成代谢中起重要作用^[28],有关研究需要进一步严谨的临床研究设计,更多样本类型、更多病种、更大样本的数据分析需要被纳入。除此之外,在健康人群中鉴别原发性肝癌时,甲胎蛋白异质体、异常凝血酶原、GPC3等被用于与AFP联合诊断。同时,许多研究再次基础上进一步探索AFP单项或多项指标进一步联合其他外周血标志物,如:血清壳多糖酶3样蛋白1^[29]、GNB4和Riplet基因甲基化检测^[30]、微RNA^[31]等,可提高AFP单项或联合甲胎蛋白异质体等的检测效能,胆汁酸与以上指标的联合检测效力也值得进一步探讨。

综上所述,原发性肝癌与转移性肝癌血浆胆汁酸含量及组成有明显差异,血浆差异性胆汁酸与肝功能及AFP呈正相关,AFP联合TBA具有潜在区分原发性肝癌与转移性肝癌的鉴别价值,对于临床诊断具有一定应用潜力。

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