



原发性胆汁性胆管炎治疗应答的影响因素及预后预测作用研究*

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【摘要】 目的 探索血脂异常的原发性胆汁性胆管炎(primary biliary cholangitis, PBC)患者对熊去氧胆酸(ursodeoxycholic acid, UDCA)治疗应答不佳的影响因素、预后特点。方法 回顾性收集2009年1月-2022年3月在四川大学华西医院治疗的512例确诊为PBC的患者。根据UDCA治疗应答情况分为完全应答组($n=305$)和UDCA应答不佳组($n=207$),对比两组患者的资料,预测影响应答的不利因素。受试者工作特征(receiver operating characteristic, ROC)曲线下面积(area under the curve, AUC)确定血清总胆固醇(total cholesterol, TC)的临界值,分析患者基线实验室检查指标、治疗后应答的差异。根据临界值将患者分为 $TC \geq 5.415$ mmol/L组与 $TC < 5.415$ mmol/L组,并使用UK-PBC、GLOBE评分评估两组预后的差异。结果 UDCA应答不佳组的基线谷丙转氨酶(alanine aminotransferase, ALT)、谷草转氨酶(aspartate aminotransferase, AST)、总胆红素(total bilirubin, TB)、碱性磷酸酶(alkaline phosphatase, ALP)、 γ -谷氨酰转肽酶(gamma-glutamyl transferase, GGT)、甘油三酯(triglyceride, TG)、TC、高密度脂蛋白胆固醇(high-density lipoprotein cholesterol, HDL-C)和低密度脂蛋白胆固醇(low-density lipoprotein cholesterol, LDL-C)较完全应答组升高(P 均 < 0.05),白蛋白水平下降($P=0.012$)。logistic回归模型多因素分析提示TC[比值比(odds ratio, OR)=1.501, 95%置信区间(confidence interval, CI): 1.275 ~ 1.767, $P < 0.01$]和ALP($OR=1.005$, 95%CI: 1.003 ~ 1.006, $P < 0.01$)是影响应答的独立风险因素。ROC曲线分析提示 $TC \geq 5.415$ mmol/L的PBC患者预后更差(AUC: 0.727, 95%CI: 0.680 ~ 0.775, 敏感性63.8%, 特异性76.4%)。另外,高TC组($TC \geq 5.415$ mmol/L)治疗1年时的UK-PBC风险评分高于低TC组($TC < 5.415$ mmol/L),差异有统计学意义($P < 0.01$)。结论 高胆固醇血症是PBC患者对UDCA应答不佳的一个独立风险因素。当基线血清 $TC \geq 5.415$ mmol/L时,PBC患者对UDCA治疗的应答及预后较差。

【关键词】 原发性胆汁性胆管炎 熊去氧胆酸 生化应答 高胆固醇血症

Response to Primary Biliary Cholangitis Treatment: Influencing Factors and the Role in Prognosis Prediction LIU Yifeng, FAN Xiaoli, SHEN Yi, MEN Ruoting, GUO Yuxin, YANG Li[△]. Department of Gastroenterology, West China Hospital, Sichuan University, Chengdu 610041, China

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【Abstract】 Objective To examine the influencing factors and prognostic features of poor response to ursodeoxycholic acid (UDCA) treatment in primary biliary cholangitis (PBC) patients with dyslipidemia. **Methods** A retrospective study was conducted, covering 512 patients who had a confirmed diagnosis of PBC, and who received treatment at West China Hospital, Sichuan University between January 2009 and March 2022. According to their actual response to UDCA treatment, patients were divided into two groups, UDCA full-response group ($n=305$) and UDCA non-responding group ($n=207$). The data from the two groups were compared to predict the adverse factors influencing patient response and the area under the curve (AUC) of the receiver operating characteristic (ROC) curve, identify the cut-off value of total cholesterol (TC), and analyze the differences in baseline laboratory test findings and the rate of responses to treatment. According to the TC cut-off value, patients were divided into a group with $TC \geq 5.415$ mmol/L and another group with $TC < 5.415$ mmol/L. In addition, differences in the prognosis of the two groups were assessed by comparing the UK-PBC and GLOBE scores. **Results** The baseline data, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TB), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), triglycerides (TG), TC, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), were significantly increased in the UDCA non-responding group compared to those in the full-response group (all $P < 0.005$), while the albumin level of the UDCA non-responding group was decreased compared to that of the full-response group ($P=0.012$). Findings of multi-factor logistic regression analysis suggested that TC (odds ratio [OR]=1.501, 95% confidence interval [CI]: 1.275-1.767, $P < 0.01$) and ALP ($OR=1.005$, 95% CI: 1.003-1.006, $P < 0.01$) were independent risk factors influencing patient response. The ROC curve analysis suggested worse prognosis for patients with $TC \geq 5.415$ mmol/L (AUC: 0.727, 95% CI: 0.680-0.775, 63.8% sensitivity, 76.4% specificity). In addition, the UK-PBC risk score

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at 1 year of treatment was higher in the high-TC group ($TC \geq 5.415$ mmol/L) than that in the low-TC group ($TC < 5.415$ mmol/L) ($P < 0.05$). **Conclusions** Hypercholesterolemia is an independent risk factor for poor response to UDCA in PBC patients. When the baseline TC is equal to or higher than 5.415 mmol/L, PBC patients have a relatively poor response to UDCA and poor prognosis.

【Key words】 Primary cholestatic cholangitis Ursodeoxycholic acid Biochemical response Hypercholesterolemia.

原发性胆汁性胆管炎(primary biliary cholangitis, PBC)是一种典型的自身免疫性肝病,发病人群以女性为主,以破坏性淋巴细胞性胆管炎和抗线粒体抗体(antimitochondrial antibody, AMA)升高为特征^[1]。PBC患者常出现血脂异常^[2]。75%~95%的PBC患者会出现高胆固醇血症^[3-5]。在早期研究中提到,与PBC相关的高胆固醇血症不会增加这些患者因心血管风险导致的死亡^[3,6-8]。近年来的研究也发现,没有足够的证据表明PBC合并高胆固醇血症患者心血管疾病的风险增加^[9]。然而,根据以往的研究,高胆固醇血症与慢性肝病患者的肝纤维化、胆汁淤积和胆石形成密切相关,血清胆固醇在PBC的发生和发展中可能具有重要的临床意义^[10]。高胆固醇血症是否会影响PBC患者对于治疗的应答,目前还没有相关研究证实。

PBC患者伴随的高胆固醇血症是否会影响其生化应答是值得关注的临床问题。熊去氧胆酸(ursodeoxycholic acid, UDCA)是目前唯一被证实可以延缓PBC进展和改善患者生存的药物。然而,大约有40%的患者对于UDCA不能完全应答^[11]。此外,UDCA会增加胆固醇的吸收,而作为PBC二线治疗的贝特类药物,可以调节胆固醇受体的结合以及改善紊乱的胆汁酸稳态^[11]。因此,有必要充分探索PBC患者高胆固醇血症和UDCA生化应答之间的关系。如何尽快发现部分不应答的患者并进行有效的联合治疗,是PBC临床诊治的一个难点。

因此,本研究探讨了PBC患者接受UDCA治疗后应答不佳的相关因素,以进一步明确血清胆固醇与PBC患者生化应答之间的联系,主要探究血清胆固醇对PBC患者生化应答的预测作用。此外,利用UK-PBC及GLOBE评分对相关临床指标、治疗应答反应进行评分,从而预测高TC组和低TC组PBC患者发生终末期肝病的风险及无肝移植生存率,比较两组间预后的差异。

1 资料和方法

1.1 研究对象

纳入2009年1月-2022年3月在四川大学华西医院治疗的PBC患者。诊断标准根据2018年美国肝病研究协会(American Association for the Study of Liver Diseases,

AASLD)发布的PBC诊断和治疗指南^[12]。确立PBC的诊断必须满足以下三个标准中的两个:①以血清碱性磷酸酶(alkaline phosphatase, ALP)升高为主的胆汁淤积生化异常;②自身抗体AMA(+),或抗sp100(+)、抗gp210(+);③组织学改变:非化脓性破坏性胆管炎和小叶间胆管破坏。纳入标准:①符合PBC诊断标准并规律服用UDCA治疗的患者;②年龄 ≥ 18 岁;③患者服用UDCA后随访至少1年。排除标准:①有肝硬化失代偿并发症,腹水、肝性脑病、食管胃底静脉曲张破裂出血等^[13];②伴有肿瘤、脂质代谢异常和其他肝病,如病毒性肝炎、自身免疫性肝炎(autoimmune hepatitis, AIH)、原发性硬化性胆管炎(primary sclerosing cholangitis, PSC)、酒精性肝病、非酒精性脂肪肝、Wilson病等;③使用UDCA治疗后随访不到6个月的患者;④没有基线胆固醇资料的患者;⑤随访不到1年死亡的患者;⑥无法获得临床或实验室数据的患者。肝硬化的诊断是依据肝脏组织学、腹部影像学,如超声、计算机断层扫描和/或磁共振成像,或内镜检查^[14]。本研究项目经四川大学华西医院伦理委员会审核批准(2013年审221号)。

1.2 研究方法

1.2.1 研究指标及分组情况

本研究中所有纳入研究的PBC患者均口服UDCA进行规范性治疗[13~15 mg/(kg·d)]。根据UDCA治疗应答情况分为完全应答组($n=305$)和UDCA应答不佳组($n=207$),对比两组患者的资料,包括年龄、性别等一般信息,血清生化指标包括反映肝功能的谷丙转氨酶(alanine aminotransferase, ALT)、谷草转氨酶(aspartate aminotransferase, AST)、ALP、 γ -谷氨酰转肽酶(gamma-glutamyl transferase, GGT)、白蛋白(albumin, ALB)、球蛋白(globulin, GLB)、总胆红素(total bilirubin, TB),以及血脂[甘油三酯(triglyceride, TG)、总胆固醇(total cholesterol, TC)、高密度脂蛋白胆固醇(high-density lipoprotein cholesterol, HDL-C)和低密度脂蛋白胆固醇(low-density lipoprotein cholesterol, LDL-C)],还有血小板(platelet, PLT)和AMA、抗核抗体(antinuclear antibody, ANA)。同时通过AST和PLT比率指数(aspartate aminotransferase/platelet ratio index)和FIB-4指数

(fibrosis-4 score, FIB-4)来评估两组患者肝纤维化程度的差异。PBC生化应答评估是在UDCA治疗1年后用巴黎 I 标准(肝硬化期)($ALP \leq 3 \times ULN$, $AST \leq 2 \times ULN$, 胆红素正常)及巴黎 II 标准(炎症期)(ALP 和 $AST \leq 1.5 \times ULN$, 胆红素正常)来评估。肝硬化期及炎症期PBC患者分别满足上述标准为完全应答,反之应答不佳。另外,通过受试者工作特征(receiver operating characteristic, ROC)曲线分析得出约登指数确定截断值将患者分成 $TC \geq 5.415$ mmol/L组(高TC组)和 $TC < 5.415$ mmol/L组(低TC组)并比较两组临床特征。自基线治疗1年后使用UK-PBC评分估计患者未来特定时间点(5、10、15年)发展为终末期肝病的风险,并使用GLOBE评分比较两组患者在未来3年、5年、10年、15年这些时间点无肝移植生存率的差异,此两种评分是近年来被使用的PBC预后模型,对患者肝移植或死亡的风险预测均具有较好的准确性。

1.2.2 统计学方法

采用百分数、中位数和四分位数间距来进行统计描述。符合正态分布的计量资料两组间比较使用 t 检验,非正态分布的计量资料两组间比较使用Mann-Whitney U 检验。计数资料两组间比较使用 χ^2 检验。通过单因素分析及多因素logistic回归分析评估与UDCA应答相关的风险因素。运用ROC曲线分析基线TC、ALP水平对UDCA预后的预测价值,通过约登指数确定TC、ALP截断值。统计软件为SPSS 25.0, $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 完全应答组与应答不佳组患者的基线特征

在本研究中,首先纳入1 069例明确诊断PBC的患者,

经过排除标准筛选后,最终纳入512例PBC患者。纳入排除过程以流程图的形式展示(图1)。

512例患者中,有40.4%(207/512)的患者在1年后被评估为UDCA应答不佳组。单因素分析提示应答不佳患者的基线ALT、AST、TB、ALP和GGT的水平高于完全应答的患者($P < 0.05$),而ALB水平低于完全应答组($P < 0.05$)。在血脂指标的比较上,应答不佳组血脂水平高于完全应答组,包括TG、TC、HDL-C和LDL-C($P < 0.05$)。见表1。

2.2 应答不良相关危险因素评估

在对患者基线指标进行单因素分析后(表1),进一步进行多因素logistic回归分析。以UDCA是否应答为因变量(0=应答,1=不应答),将ALT、AST、TB、ALB、ALP、GGT、TG、TC、HDL-C和LDL-C等指标($P < 0.10$)作为自变量且直接以连续型变量纳入回归模型。经非条件多因素logistic回归模型分析得出结果,TC[比值比(odds ratio, OR)=1.501, 95%置信区间(confidence interval, CI): 1.275 ~ 1.767, $P < 0.01$]和ALP(OR=1.005, 95%CI: 1.003 ~ 1.006, $P < 0.01$)是影响应答及预后的独立风险因素,ALB(OR=0.960, 95%CI: 0.929 ~ 0.992, $P = 0.015$)为保护性因素。见表2。

2.3 基线血清TC水平可预测PBC患者UDCA治疗的预后

由于高胆固醇血症与UDCA治疗1年后的生化应答有关,因此进行ROC曲线分析,分析基线TC水平对UDCA应答的预测价值(图2A)。曲线下面积(area under the curve, AUC)为0.727(95%CI: 0.680 ~ 0.775, $P < 0.001$),截断值为血清胆固醇水平5.415 mmol/L(敏感性63.8%,特异性76.4%)。此外,ALP的ROC曲线显示(图2B),

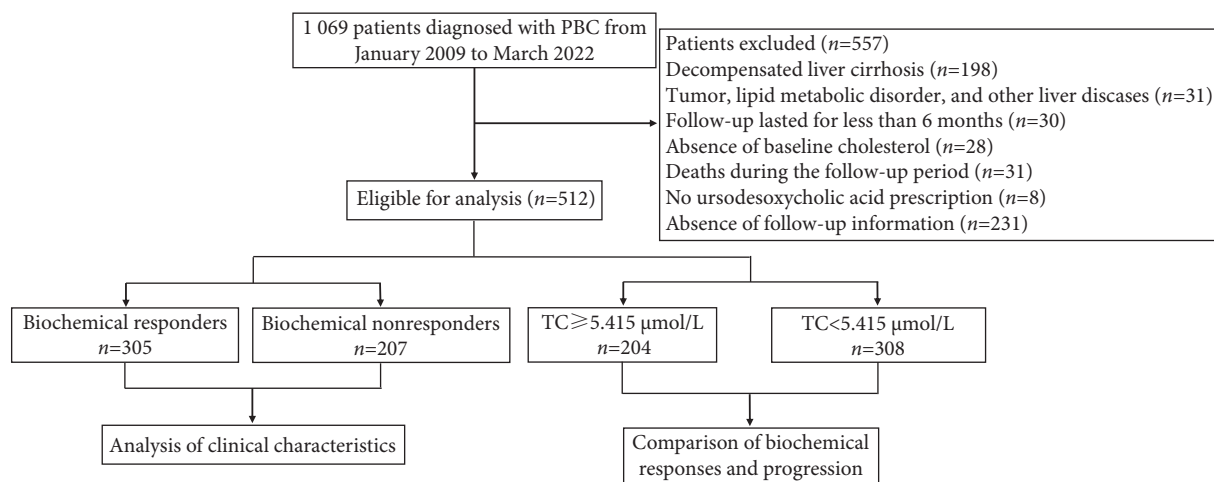


图1 患者纳入排除及分析流程图

Fig 1 Flowchart of the patient inclusion and exclusion process

PBC: primary biliary cholangitis; TC: total cholesterol.

表 1 应答组与应答不佳组基线临床特征比较

Table 1 Comparison of baseline clinical characteristics of the responding and non-responding groups

Variable	Responders (n=305)	Nonresponders (n=207)	P
(Female/male)/case	268/37	183/24	0.854
Age/yr., $\bar{x} \pm s$	53.13±11.24	52.57±10.09	0.566
TB/($\mu\text{mol/L}$), median (IQR)	15.0 (8.9)	19.2 (19.9)	0.005
ALT/(IU/L), median (IQR)	45.0 (47.5)	68.0 (61.0)	<0.001
AST/(IU/L), median (IQR)	48.0 (38.0)	73.0 (49.0)	0.003
ALB/(g/L), median (IQR)	45.2 (5.6)	43.7 (6.3)	0.012
GLB/(g/L), median (IQR)	32.7 (7.7)	33.6 (6.9)	0.375
ALP/(IU/L), median (IQR)	157 (132)	307 (243)	<0.001
GGT/(IU/L), median (IQR)	145 (204)	310 (417)	<0.001
TG/(mmol/L), median (IQR)	1.20 (0.64)	1.33 (0.85)	0.003
TC/(mmol/L), median (IQR)	4.83 (1.25)	5.93 (2.05)	<0.001
HDL-C/(mmol/L), median (IQR)	1.57 (0.61)	1.76 (0.89)	0.004
LDL-C/(mmol/L), median (IQR)	2.61 (1.04)	3.06 (1.33)	<0.001
PLT/($\times 10^9 \text{ L}^{-1}$), median (IQR)	147 (109)	153 (100)	0.652
AMA (+)/case (%)	180 (59.0)	120 (57.9)	0.814
Cirrhosis/case (%)	79 (25.9)	45 (21.7)	0.281
Fib-4 (median [IQR])	2.55 (3.49)	3.06 (3.17)	0.726
ABRI (median [IQR])	0.99 (1.39)	1.38 (1.25)	0.782

TB: total bilirubin; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALB: albumin; GLB: globulin; ALP: alkaline phosphatase; GGT: gamma-glutamyl transferase; TG: triglyceride; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; PLT: platelet; AMA: anti-mitochondrial antibody; Fib-4: fibrosis score; APRI: aspartate aminotransferase/platelet ratio index.

表 2 影响UDCA应答的多因素logistic回归分析

Table 2 Logistic regression analysis of multiple factors affecting UDCA response

Parameter	β	SE	P	OR	95% CI
TB/($\mu\text{mol/L}$)	-0.001	0.004	0.853	0.999	0.991-1.007
ALT/(IU/L)	-0.002	0.004	0.634	0.998	0.990-1.006
AST/(IU/L)	-0.002	0.005	0.611	0.998	0.998-0.993
ALB/(g/L)	-0.041	0.017	0.015	0.960	0.929-0.992
ALP/(IU/L)	0.005	0.001	<0.001	1.005	1.003-1.006
GGT/(IU/L)	<0.001	0.001	0.906	1.000	0.999-1.001
TG/(mmol/L)	0.069	0.160	0.667	1.071	0.783-1.465
TC/(mmol/L)	0.406	0.083	<0.001	1.501	1.275-1.767
HDL-C/(mmol/L)	0.003	0.250	0.991	1.003	0.615-1.636
LDL-C/(mmol/L)	-0.217	0.247	0.380	0.805	0.496-1.306

The abbreviations are explained in the note to Table 1. β : regression coefficient; SE: standard error; OR: odds ratio; CI: confidence interval.

AUC为0.783(95%CI: 0.743 ~ 0.823, $P < 0.001$), 截断值为222.5 UI/L(敏感性75.8%, 特异性70.5%)。如表3所示, 根据血清胆固醇截断值(5.415 mmol/L)将患者分为低TC组(308/512, 60.2%)与高TC组(204/512, 39.8%), 低TC组中应答率(75.6%, 233/308)高于高TC组(35.3%, 72/204,

$P < 0.01$)。此外, 高TC组ALT、AST、TB、ALP、GGT、TG和LDL-C均高于低TC组($P < 0.05$), HDL-C、PLT低于后者($P < 0.05$)。高TC组治疗1年后UK-PBC风险评分高于低TC组(5、10和15年, $P < 0.01$; 表4)。然而, 两组之间GLOBE评分差异无统计学意义(3、5、10、15年, $P > 0.05$; 表5)。

3 讨论

约75% ~ 95%的PBC患者有高胆固醇血症^[1], 近年来发现胆固醇代谢和胆汁酸转运在PBC的发生和发展中起着关键作用^[9]。以往研究多关注于伴有高胆固醇血症的PBC患者心血管风险的评估^[3-4]。本研究首次探讨了PBC患者血清胆固醇水平与UDCA应答之间的相关性, 有助于进一步了解血清胆固醇与PBC治疗应答以及预后的关系。

PBC的应答与预后相关^[11], 目前也有多种评估PBC应答的标准以及预测PBC预后的模型^[15]。对于PBC的生化应答影响因素, 有研究观察到ALP与PBC蛋白质组的成分有明显的相关性, 同时也提示趋化因子配体20(C-C chemokine ligand 20, CCL20)和C-X-C基序趋化因子11(C-X-C motif chemokine 11, CXCL11)炎症因子可能是评估UDCA应答的潜在标志物^[16-17]。其他影响应答的因

表 3 低TC组与高TC组临床特征比较

Table 3 Comparison of clinical features of the low TC and the high TC groups

Variable	TC<5.415 mmol/L (n=308)	TC≥5.415 mmol/L (n=204)	P
(Female/male)/case	270/38	181/23	0.716
Age/yr., $\bar{x} \pm s$	53.2±11.4	52.3±9.6	0.328
TB/($\mu\text{mol/L}$), median (IQR)	15.4 (10.7)	17.0 (16.4)	0.012
ALT/(IU/L), median (IQR)	45.0 (41.0)	70.5 (68.7)	<0.001
AST/(IU/L), median (IQR)	51.0 (39.7)	71.5 (51.7)	0.011
ALB/(g/L), median (IQR)	44.6 (5.9)	44.4 (5.8)	0.889
GLB/(g/L), median (IQR)	33.1 (7.8)	32.9 (6.7)	0.736
ALP/(IU/L), median (IQR)	172.5 (149.0)	298.0 (252.2)	<0.001
GGT/(IU/L), median (IQR)	145.0 (204.0)	336.5 (429.2)	<0.001
TG/(mmol/L), median (IQR)	1.14 (0.60)	1.54 (0.93)	<0.001
TC/(mmol/L), median (IQR)	4.55 (1.08)	6.29 (1.63)	<0.001
HDL-C/(mmol/L), median (IQR)	1.53 (0.61)	1.93 (0.96)	<0.001
LDL-C/(mmol/L), median (IQR)	2.38 (0.85)	3.49 (1.09)	<0.001
PLT/($\times 10^9 \text{L}^{-1}$), median (IQR)	136.0 (105.7)	171.5 (94.7)	0.001
AMA (+)/case (%)	184 (59.7)	116 (56.9)	0.518
Cirrhosis/case (%)	76 (24.7)	48 (23.5)	0.767
Fib-4 (median [IQR])	2.94 (4.02)	2.55 (2.15)	0.259
ABRI (median [IQR])	1.08 (1.49)	1.24 (1.27)	0.976
Response (+)/case (%)	233.0 (75.6)	72.0 (35.3)	<0.010

The abbreviations are explained in the note to Table 1. Continuous variables are presented as the median (interquartile range) and categorical variables, percentages.

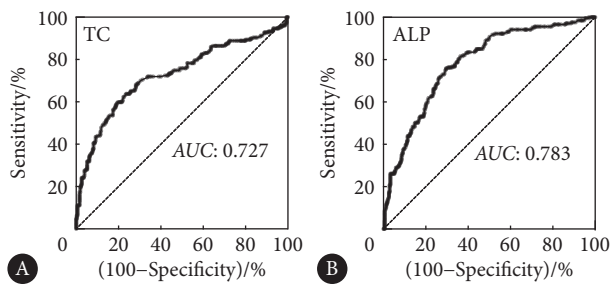


图 2 ROC曲线分析

Fig 2 Analysis of ROC curves

The abbreviations are explained in the note to Table 1.

表 4 低TC组与高TC组UK-PBC评分比较

Table 4 Comparison of the UK-PBC risk scores between low TC and the high TC groups

Predicted time	UK-PBC risk score, median (IQR)		P
	TC<5.415 (mmol/L) (n=308)	TC≥5.415 (mmol/L) (n=204)	
5 years	0.011 (0.017)	0.014 (0.028)	<0.01
10 years	0.036 (0.057)	0.046 (0.090)	<0.01
15 years	0.066 (0.102)	0.084 (0.158)	<0.01

Data are expressed as the median (interquartile range).

表 5 低TC组与高TC组GLOBE评分比较

Table 5 Comparison of the GLOBE scores between the low TC and the high TC groups

Predicted time	GLOBE score, median (IQR)		P
	TC<5.415 (mmol/L) (n=308)	TC≥5.415 (mmol/L) (n=204)	
3 years	0.960 (0.058)	0.959 (0.053)	0.315
5 years	0.930 (0.100)	0.928 (0.092)	0.320
10 years	0.824 (0.233)	0.819 (0.211)	0.320
15 years	0.707 (0.350)	0.699 (0.312)	0.312

Data are presented as the median (interquartile range).

素包括重叠综合征^[18]、肝硬化程度、门静脉高压症^[19]等。本研究发现基线高胆固醇血症是PBC患者UDCA应答不良的独立风险因素。UK-PBC评分提示基线血清胆固醇水平高于5.415 $\mu\text{mol/L}$ 的PBC患者发生终末期肝病事件的风险明显更高。

肝脏是体内胆固醇-胆汁酸代谢的主要部分,胆固醇代谢与胆汁酸代谢密切相关^[20-21]。胆固醇在肝脏中转化为胆汁酸是胆固醇代谢的主要方式。当胆汁酸平衡调节系统出现异常时,胆汁酸代谢就会出现紊乱,从而引发和

诱发肝细胞凋亡和肝纤维化,继而导致肝肠循环紊乱,最终导致胆固醇代谢紊乱^[22]。在早期的研究中,约50%的PBC患者其血浆中总胆固醇水平高于正常人^[23]。另外一项针对284例PBC患者的研究中指出76%无症状患者出现TC水平的增高,而有症状患者中有96%出现高胆固醇血症,且有症状的患者血浆中总胆固醇普遍高于无症状者^[5]。PBC并发高胆固醇血症的具体机制尚未完全阐明,在疾病早期可能的原因为PBC患者由于小胆管的破坏或梗阻导致胆汁淤积进而使胆固醇排出受阻。其他原因可能是PBC疾病进展过程中3-羟基-3-甲基戊二酸单酰辅酶A还原酶活性增强从而导致胆固醇合成增加^[24]。

UDCA是治疗PBC的一线药物^[12]。目前认为,UDCA主要是改变胆汁积聚中的胆汁酸成分以降低胆汁的毒性,稳定胆管上皮细胞的膜以抑制胆管上皮细胞的凋亡,并参与调节自身免疫反应^[1]。笔者推测,高胆固醇血症患者胆固醇代谢中重要的限速酶(例如HMG-CoA还原酶)的活性降低或失活,导致胆汁酸合成减少。大量的胆汁酸合成的原料或代谢中间体在体内积累,导致对UDCA治疗的应答不佳。

UDCA应答不佳的患者的治疗是PBC临床研究中的一个主要问题。近年来,过氧化物酶增殖体激活受体 α 激动剂(非诺贝特)和法尼醇X受体(farnesoid X Receptor, FXR)激动剂(奥贝胆酸、鹅去氧胆酸等)在针对UDCA应答不佳患者联合治疗的研究中成为热点^[25-27]。FXR是一种胆汁酸受体,其靶基因编码的成纤维细胞生长因子19(fibroblast growth factor 19, FGF19)在高胆固醇血症患者的血清中远高于对照组,且可降低高胆固醇血症造模小鼠循环中神经酰胺和胆固醇的水平^[28-29]。在FXR基因敲除的小鼠中,高脂肪饮食会诱发严重的肝脏脂肪变性、坏死性炎症和纤维化,当用FXR激动剂时,这种情况可以被逆转^[30]。此外,在一项美国大型多中心回顾性队列研究中,纳入了72 944例诊断为肝硬化的退伍军人,研究发现他汀类药物的使用与Child-Turcotte-Pugh A级和B级肝硬化患者的死亡率降低有关^[31]。近年的一项随机对照试验中纳入了158例肝硬化和门脉高压的患者,随机服用辛伐他汀,研究结果显示辛伐他汀组的死亡率(9%)明显低于安慰剂组(22%)^[32]。既往研究也提到,他汀类药物的使用并不会影响PBC患者对UDCA的应答^[33]。因此,是否可以在伴有高胆固醇血症的PBC患者中扩大适应征使用降脂药物来增加应答,值得进一步研究。

虽然本研究首次探索了血清胆固醇水平与PBC患者治疗应答的关系,但仍存在很多局限性。由于本研究为单中心的回顾性研究,证据的强度有限,且没有独立的验

证队列。本研究的结论需要通过前瞻性队列的数据来证实。虽然本研究的队列规模比较大,但仍需要一个具有更大样本量的多中心研究来证实我们的结果。此外,未来还需要进一步的基础实验研究来探索高胆固醇血症影响PBC的生化应答的具体机制。

* * *

作者贡献声明 刘一锋和凡小丽负责论文构思,门若庭和沈怡负责数据审编,刘一锋负责正式分析、研究方法、软件、初稿写作和审读与编辑写作,郭雨欣负责经费获取,杨丽负责提供资源和监督指导。所有作者已经同意将文章提交给本刊,且对将要发表的版本进行最终定稿,并同意对工作的所有方面负责。

利益冲突 所有作者均声明不存在利益冲突

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