·论著·

甲胎蛋白阴性肝癌患者血清E-cadherin、TXNIP、DKK1水平及其联合检测对预后的预测价值

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摘要 **目的** 探讨甲胎蛋白阴性肝细胞癌（AFP-NHCC）患者血清上皮钙黏蛋白（E-cadherin）、硫氧还蛋白相互作用蛋白（TXNIP）、Dickkopf相关蛋白1（DKK1）水平及其联合检测对预后的预测价值。**方法** 前瞻性分析我院接受肝癌切除术的295例AFP-NHCC患者的临床资料和术前血清E-cadherin、TXNIP、DKK1水平。随访3年，应用Cox回归分析AFP-NHCC患者预后。**结果** BCLC分期B~C期、病理低分化程度、伴肝内淋巴结转移及血清E-cadherin<886.35 μg/L、TXNIP<40.27 pg/mL、DKK1≥9.75 μg/L是影响AFP-NHCC患者预后的危险因素（$P<0.05$）；与低E-cadherin组、低TXNIP组、高DKK1组及联合高风险组相比，高E-cadherin组、高TXNIP组、低DKK1组及联合低风险组患者的累积生存率更高（均$P<0.05$）。**结论** 血清E-cadherin、TXNIP、DKK1水平与AFP-NHCC预后密切相关，且三者联合检测对患者的预后有较高预测价值。

关键词 肝细胞癌；甲胎蛋白；上皮钙黏蛋白；硫氧还蛋白相互作用蛋白；Dickkopf相关蛋白1；预后
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Serum E-cadherin, TXNIP, and DKK1 levels in patients with alpha-fetoprotein-negative hepatocellular carcinoma and their combined prognostic value

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Abstract **Objective** To investigate the serum epithelial cadherin (E-cadherin), thioredoxin-interacting protein (TXNIP), and Dickkopf-related protein 1 (DKK1) levels in patients with alpha-fetoprotein (AFP)-negative hepatocellular carcinoma (NHCC) and their combined prognostic value. **Methods** The clinical data of 295 patients with AFP-NHCC who underwent liver cancer resection at our hospital and their preoperative serum E-cadherin, TXNIP, and DKK1 levels were retrospectively analyzed. After 3 years of follow-up, the prognosis of the patients with AFP-NHCC was analyzed using Cox regression. **Results** Cox regression analysis showed that Barcelona Clinic Liver Cancer stage B to C, poor pathological differentiation, intrahepatic lymph node metastasis, and serum levels of E-cadherin (<886.35 μg/L), TXNIP (<40.27 pg/mL), and DK1 (≥9.75 μg/L) were prognostic factors in patients with AFP-NHCC ($P<0.05$). The Kaplan-Meier curve showed that the high E-cadherin, high TXNIP, low DKK1, and joint low-risk groups had higher cumulative survival rates than the low E-cadherin, low TXNIP, high DKK1, and joint high-risk groups (all $P<0.05$). **Conclusion** Serum E-cadherin, TXNIP, and DKK1 levels are closely associated with the prognosis of AFP-NHCC, and their combination demonstrated high predictive value for patient prognosis.

Keywords hepatocellular carcinoma; alpha-fetoprotein; epithelial cadherin; thioredoxin-interacting protein; Dickkopf-related protein 1; prognosis

肝细胞癌（hepatocellular carcinoma，HCC）早期不易发现，大多数患者确诊时病情已进展为晚期，5年生存率较低[1-2]。甲胎蛋白（alpha-fetoprotein，AFP）是评估HCC患者预后的血清肿瘤标志物，然而因AFP的灵敏度较低（仅40%~65%），诊断特异度76%~96%，导致部分患者预后不佳[3-4]。AFP阴性HCC（alpha-fetoprotein-negative hepatocellular carcinoma，AFP-NHCC）是指HCC患者的AFP水平处于阴性参考范围（AFP < 20 μg/L）[5]。上皮钙黏蛋白（epithelial cadherin，E-cadherin）是一种钙黏附分子，在钙离子作用下介导或调节上皮细胞间、细胞与基质间的黏附反应，对维持细胞组织结构形态、完整性起关

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键作用[6-7]。硫氧还蛋白相互作用蛋白(thioredoxin-interacting protein,TXNIP)是一种具有氧化还原活性的抑癌蛋白,能负向调控硫氧还蛋白活性,引起氧化应激损伤,导致细胞凋亡[8-9]。Dickkopf相关蛋白1(Dickkopf-related protein 1,DKK1)是分泌型糖蛋白Dickkopf家族成员之一,通过阻滞Wnt/β-catenin信号通路参与调节肿瘤细胞迁移分化、侵袭与血管形成等[10-11]。目前有关血清E-cadherin、TXNIP、DKK1水平对AFP-NHCC患者预后的预测价值研究鲜有报道。本研究通过检测AFP-NHCC患者血清E-cadherin、TXNIP、DKK1水平,分析三者及其联合检测对AFP-NHCC患者预后的预测价值,旨在为临床提供参考。

1　材料与方法

1.1　一般资料

收集2018年6月至2021年6月就诊于我院的295例AFP-NHCC患者的临床资料。其中,男198例,女97例;年龄(62.46±6.25)岁。纳入标准:接受手术治疗;术前血清AFP<20 μg/L;经计算机断层扫描(computed tomograghy,CT)或磁共振成像(magnetic resonance imaging,MRI)等影像学检查,并结合血清AFP检测结果诊断为AFP-NHCC;初次治疗;既往无其他消化系统疾病;基线资料完整。排除标准:已接受放化疗;伴其他恶性肿瘤及远处转移;合并血液系统疾病、急性感染性疾病。本研究获得唐山中心医院伦理委员会批准(20240072)。所有患者知情同意。

1.2　方法

1.2.1　收集临床资料:通过医院电子病历系统收集患者的临床资料,包括性别、年龄、肿瘤最大径、肿瘤结节数目、包膜完整性、肝癌巴塞罗那(Barcelona Clinic Liver Cancer,BCLC)分期、病理分化程度、肝内淋巴结转移及血清E-cadherin、TXNIP、DKK1水平等。术前采集患者空腹静脉血,应用酶联免疫吸附试验检测血清E-cadherin、TXNIP、DKK1水平。

1.2.2　随访:以门诊、电话等形式随访(每3个月1次),共随访3年。随访内容包括患者的生存状态,肿瘤复发情况,肝功能指标(如丙氨酸氨基转移酶、天冬氨酸氨基转移酶、胆红素等),以及影像学检查(如腹部CT/MRI)等。总生存期(overall survival,OS)为手术至死亡或随访结束的时间。

1.3　统计学分析

采用SPSS 26.0软件统计分析数据。计数资料用率(%)表示,采用χ^2检验进行比较。采用受试者操作特征(receiver operating characteristic,ROC)曲线分析血清E-cadherin、TXNIP、DKK1水平的最佳临界值,以获得曲线下面积(area under the curve,AUC)和置信区间(confidence interval,*CI*)。应用Cox比例风险回归分析影响因素,并计算风险比(hazard ratio,*HR*)和95%*CI*。应用Kaplan-Meier法及log-rank检验评估OS生存曲线的差异性。均进行双侧检验,检验水准α=0.05。

2　结果

2.1　影响AFP-NHCC患者预后的因素

单因素分析显示,BCLC分期、病理分化程度、伴肝内淋巴结转移及血清E-cadherin、TXNIP、DKK1水平与AFP-NHCC患者预后较差相关($P<0.05$)。进一步将BCLC分期(B~C期=1,0~A期=0),病理分化程度(低分化=1、中高分化=0),肝内淋巴结转移(有=1,无=0),E-cadherin(<886.35 μg/L=1,≥886.35 μg/L=0)、TXNIP(<40.27 pg/mL=1,≥40.27 pg/mL=0)、DKK1(≥9.75 μg/L=1,<9.75 μg/L=0)作为自变量,以AFP-NHCC患者的生存预后为因变量(死亡=1,存活=0),纳入多因素Cox回归分析,结果显示,AFP-NHCC患者的预后不良可能与BCLC分期B~C期、病理低分化程度、伴有肝内淋巴结转移及血清E-cadherin低水平、TXNIP低水平、DKK1高水平有关($P<0.05$)。见表1、表2。

2.2　血清E-cadherin、TXNIP、DKK1水平的最佳临界值

根据ROC曲线,计算血清E-cadherin、TXNIP、DKK1水平预测AFP-NHCC患者生存预后的最佳截断值。E-cadherin为886.35 μg/L(AUC=0.728,95%*CI*:0.685~0.824)。TXNIP为40.27 pg/mL(AUC=0.712,95%*CI*:0.674~0.839)。DKK1为9.75 μg/L(AUC=0.743,95%*CI*:0.689~0.872)。三者联合的AUC为0.874(95%*CI*:0.788~0.946),差异有统计学意义($P<0.05$)。见图1。

2.3　血清E-cadherin、TXNIP、DKK1水平对AFP-NHCC患者预后生存曲线的影响

根据血清E-cadherin、TXNIP、DKK1水平的最佳临界值,将患者分为低E-cadherin组($n=54$)和高E-cadherin组($n=241$),低TXNIP组($n=55$)和高TXNIP组($n=240$),低DKK1组($n=242$)和高DKK1组($n=$

53）。联合3个指标分组，将患者分为联合低风险组（$n=237$，均符合高E-cadherin、高TXNIP及低DKK1）和联合高风险组（$n=58$，均符合低E-cadherin、低TXNIP及高DKK1）。

表1　单因素分析结果

Tab.1　Univariate analysis results

Variate	β	*SE*	Wald χ^2	*HR*（95%*CI*）	*P*
Sex	0.611	0.362	2.849	1.842（0.906–3.745）	0.092
Age	0.597	0.356	2.720	1.817（0.894–3.693）	0.100
Tumor maximum diameter	0.575	0.351	2.523	1.777（0.874–3.613）	0.113
Number of tumor nodules	0.624	0.373	2.971	1.866（0.918–3.794）	0.085
Capsid integrity	0.605	0.368	2.793	1.831（0.901–3.723）	0.095
BCLC staging	0.972	0.436	7.210	2.643（1.300–5.374）	0.008
Pathological differentiation degree	1.023	0.461	7.986	2.782（1.368–5.655）	0.005
Intrahepatic lymph node metastasis	1.154	0.486	10.162	3.171（1.560–6.446）	0.002
E-cadherin	–0.963	0.422	7.077	0.382（0.188–0.776）	0.008
TXNIP	–0.927	0.401	6.558	0.396（0.195–0.805）	0.011
DKK1	1.167	0.493	10.393	3.212（1.580–6.531）	0.002

表2　多因素分析结果

Tab.2　Multivariate analysis results

Variate	β	*SE*	Wald χ^2	*HR*（95%*CI*）	*P*
BCLC staging	0.862	0.384	5.670	2.368（1.165–4.814）	0.018
Pathological differentiation degree	0.913	0.396	6.361	2.492（1.226–5.066）	0.012
Intrahepatic lymph node metastasis	1.243	0.527	11.790	3.466（1.705–7.046）	0.001
E-cadherin	–0.867	0.371	5.736	0.420（0.207–0.854）	0.017
TXNIP	–0.825	0.364	5.194	0.438（0.216–0.891）	0.023
DKK1	1.065	0.413	8.655	2.901（1.427–5.897）	0.003

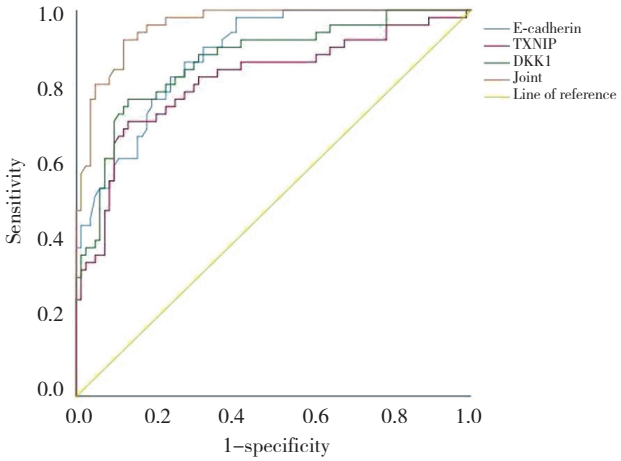


图1　血清E-cadherin、TXNIP、DKK1水平的ROC曲线

Fig.1　ROC curves of serum E-cadherin，TXNIP and DKK1 levels

随访3年，无失访患者，共60例患者死亡。通过Kaplan-Meier分析获取生存曲线，结果显示，在随访第1、2、3年，高E-cadherin组和低E-cadherin组死亡患者数量分别为5、21、15例和3、10、6例，高TXNIP组和低TXNIP组分别为2、21、17例和4、9、7例，低DKK1组和高DKK1组分别为3、24、14例和2、12、5例，联合低风险组和联合高风险组分别为1、26、13例和4、9、7例。与低E-cadherin组（64.81%）、低TXNIP组（63.64%）、高DKK1组（64.15%）及联合高风险组（65.52%）相比，高E-cadherin组（82.99%）、高TXNIP组（83.33%）、低DKK1组（83.06%）及联合低风险组（83.12%）患者的累积生存率较高（$\chi^2=8.992$、10.715、9.593、8.914，均$P<0.05$）。

3　讨论

AFP-NHCC是临床常见的消化系统肿瘤之一，其发病较为隐匿，全球发病率和致死率较高[12-13]。研究[14-15]表明，血清AFP水平对HCC患者预后的不良影响与肿瘤侵袭行为密切相关，但对于AFP-

NHCC患者的灵敏度不高，导致AFP在HCC患者的预后评估中应用受限。因此，临床上迫切需要寻找用于术前判断AFP-NHCC患者预后的血清学标志物。

E-cadherin通过激活β连环蛋白信号途径，参与肿瘤细胞迁移、生长，在肿瘤的发生、发展过程中发挥关键作用，E-cadherin表达水平越低，肿瘤的侵袭转移能力越强[16]。TXNIP在多种肿瘤组织中呈现低表达状态，可与Trx结合，抑制其抗氧化活性，与肿瘤恶性进展及患者的预后密切相关[17-18]。DKK1是Wnt信号通路的负性调控蛋白，在多种肿瘤患者血清中呈高表达，在肿瘤细胞增殖、分化以及凋亡等过程中起重要作用[19]。本研究结果显示，AFP-NHCC患者的不良预后可能与BCLC分期B~C期、病理低分化程度、伴肝内淋巴结转移及血清E-cadherin低水平、TXNIP低水平、DKK1高水平有关。分析其可能的原因如下：(1) BCLC分期严重，病理分化程度低，且伴有远处转移时，提示病情逐渐向晚期进展，肿瘤细胞侵袭能力进一步增强[20-21]；(2) E-cadherin表达水平降低可增加内皮细胞通透性，损害内皮连接完整性，增强肿瘤细胞的增殖、抗凋亡能力，促进肿瘤细胞转移、侵袭[22]；(3) TXNIP表达水平降低可能抑制线粒体相关的凋亡通路，通过启动凋亡信号调节激酶1，传导细胞凋亡信号，并促进肿瘤细胞增殖、迁移及转移[23]；(4) 血清DKK1水平升高，能通过竞争方式与细胞表面受体LRP5/6结合，调控Wnt/β-catenin连环蛋白信号转导通路，拮抗下游靶基因表达，抑制肿瘤细胞凋亡，发挥促癌因子作用[24]。

本研究中，Kaplan-Meier生存曲线分析显示，高E-cadherin组、高TXNIP组、低DKK1组及联合低风险组患者的累积生存率高于低E-cadherin组、低TXNIP组、高DKK1组及联合高风险组。说明血清E-cadherin、TXNIP、DKK1及其联合检测对AFP-NHCC患者的预后具有一定的预测价值。

综上所述，血清E-cadherin、TXNIP、DKK1水平与AFP-NHCC患者的预后密切相关，三者联合检测对预后有较高的预测价值。

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