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【临床研究】

术前CT定量参数与肝动脉化疗栓塞术后肝癌患者预后的相关性 及预后预测列线图模型的构建

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摘要: **目的** 探讨术前CT定量参数与肝动脉化疗栓塞术(TACE)后肝癌患者预后的相关性,并构建预后预测列线图模型。**方法** 选择2020年5月至2022年5月于濮阳市第五人民医院医学影像科行TACE治疗的120例肝癌患者为研究对象。术前均完善螺旋CT平扫及灌注成像扫描,测定肝血流量(HBF)、肝动脉灌注量(HAP)、门静脉灌注量(PVP)、肝动脉灌注指数(HAI)、平均通过时间(MTT)等CT定量参数。术后随访至2023年5月,根据临床转归将患者分为预后良好组($n=90$)和预后不良组($n=30$),比较2组患者的性别、年龄、体质指数(BMI)、吸烟酗酒史、TNM分期、肿瘤最大径、肿瘤数目、包膜是否完整、白蛋白、血小板、总胆红素、白细胞计数、丙氨酸氨基转移酶(ALT)、天冬氨酸氨基转移酶(AST)、甲胎蛋白(AFP)及HBF、HAP、HAI、MTT;采用logistic多因素回归分析影响经TACE治疗肝癌患者预后的危险因素,应用R软件基于筛选出的CT定量参数构建经TACE治疗肝癌患者预后预测列线图模型,应用rms程序包和Bootstrap内部验证法验证该模型预测经TACE治疗肝癌患者预后不良的效能。**结果** 预后不良组患者TNM分期Ⅲ~Ⅳ期占比、包膜不完整占比及AFP、HBF、HAP、HAI水平显著高于预后良好组,MTT显著短于预后良好组($P<0.05$);预后不良组与预后良好组患者的性别构成、年龄、BMI、吸烟史比例、肿瘤最大径 >5 cm占比、肿瘤数目 >1 个占比、白蛋白水平、血小板计数、总胆红素水平、ALT水平、AST水平、PVP比较差异无统计学意义($P>0.05$)。Logistic多因素回归分析结果显示,包膜不完整[比值比(OR)=2.202,95%置信区间(CI):1.884~2.880, $P=0.000$]、AFP水平高($OR=2.187$,95% CI :1.818~2.787, $P=0.000$)、HBF高($OR=2.177$,95% CI :1.859~2.862, $P=0.000$)、HAP高($OR=2.192$,95% CI :1.907~2.909, $P=0.000$)、HAI高($OR=2.212$,95% CI :1.926~2.816, $P=0.000$)、MTT短($OR=2.208$,95% CI :1.927~2.954, $P=0.000$)是影响经TACE治疗肝癌患者预后的危险因素。基于HBF、HAP、HAI、MTT构建经TACE治疗肝癌患者预后预测列线图模型,该模式实测值与预测值结果基本一致,具有良好的预测性能;C-index为0.908(95% CI :0.787~0.968),该模型区分度及准确度较好。**结论** HBF、HAP、HAI、MTT是影响TACE后肝癌患者预后的危险因素,基于HBF、HAP、HAI和MTT构建的列线图模型对经TACE治疗肝癌患者预后预测效能较高。

关键词: 肝癌;肝动脉化疗栓塞术;预后;CT定量参数;列线图模型

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Correlation between preoperative CT quantitative parameters and prognosis of patients with liver cancer treated with transcatheter arterial chemoembolization and construction of nomogram model for prognostic prediction

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Abstract: **Objective** To investigate the correlation between preoperative CT quantitative parameters and the prognosis of patients with liver cancer treated by transcatheter arterial chemoembolization (TACE), and to construct a nomogram model for prognostic prediction. **Methods** A total of 120 patients with liver cancer who received TACE treatment in the Department of Medical Imaging, the Fifth People's Hospital of Puyang City from May 2020 to May 2022 were selected as the research subjects. Spiral CT plain scan and perfusion imaging were performed before surgery, and CT quantitative parameters such as hepatic blood flow (HBF), hepatic artery perfusion (HAP) volume, portal vein perfusion (PVP) volume, hepatic arterial infusion (HAI) index and mean transit time (MTT) were measured. These patients were followed up to May 2023, and according to clinical outcomes, they were divided into the good prognosis group ($n=90$) and the poor prognosis group ($n=30$). Gender, age, body mass index (BMI), history of smoking and alcoholism, TNM stage, maximum tumor size, tumor number, complete or

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incomplete envelope, albumin, platelets, total bilirubin, white blood cell count, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alpha-fetoprotein (AFP), HBF, HAP, HAI, and MTT were compared between the two groups. The risk factors affecting the prognosis of liver cancer patients treated with TACE were analyzed by logistic multivariate regression. CT quantitative parameters were screened out by R software to construct a nomogram model for predicting the prognosis of liver cancer patients treated by TACE. The efficiency of this model in predicting the poor prognosis of liver cancer patients treated by TACE was verified by the rms package and Bootstrap internal validation method. **Results** The proportion of TNM stages III-IV, the proportion of incomplete envelope and the levels of AFP, HBF, HAP and HAI in the poor prognosis group were significantly higher than those in the good prognosis group, while MTT in the poor prognosis group was significantly shorter than that in the good prognosis group ($P < 0.05$). There was no significant difference in gender composition, age, BMI, smoking ratio, ratio of maximum tumor diameter > 5 cm, ratio of tumor number > 1 , albumin level, platelet count, total bilirubin level, ALT level, AST level and PVP between the poor prognosis group and the good prognosis group ($P > 0.05$). Logistic multivariate regression analysis showed that the incomplete envelope [odds ratio (OR) = 2.202, 95% confidence interval (CI): 1.884 - 2.880, $P = 0.000$], high AFP level (OR = 2.187, 95% CI: 1.818 - 2.787, $P = 0.000$), high HBF (OR = 2.177, 95% CI: 1.859 - 2.862, $P = 0.000$), high HAP (OR = 2.192, 95% CI: 1.907 - 2.909, $P = 0.000$), high HAI (OR = 2.212, 95% CI: 1.926 - 2.816, $P = 0.000$), and short MTT (OR = 2.208, 95% CI: 1.927 - 2.954, $P = 0.000$) were the risk factors affecting the prognosis of patients with liver cancer treated by TACE. The measured results were basically consistent with the predicted results based on the nomogram model constructed based on HBF, HAP, HAI and MTT, indicating that the model had good predictive performance. The C-index was 0.908 (95% CI: 0.787-0.968), indicating that the model had good differentiation and accuracy. **Conclusion** HBF, HAP, HAI and MTT are risk factors that affect the prognosis of patients with liver cancer treated by TACE. The nomogram model constructed based on the above four CT quantitative parameters has high predictive efficacy.

Key words: liver cancer; transcatheter arterial chemoembolization; prognosis; CT quantitative parameters; nomogram model

肝癌具有“高发病率、高致死率”等特征,常见致病原因有肝硬化、病毒性肝炎、黄曲霉素感染等,早期无明显症状,随疾病进展出现肝区疼痛、肝脏进行性增大、乏力消瘦时,往往已处于中晚期^[1-4]。肝动脉化学治疗栓塞术(transhepatic arterial chemoembolization, TACE)是针对不可行肝切除术的中晚期肝癌患者常用的治疗手段之一,其优势在于经导管将化学治疗药物与栓塞剂注入肿瘤供血靶动脉,栓塞靶动脉血管后达到抗癌作用;TACE治疗肝癌疗效确切、不良反应少,但术后肿瘤复发一直困扰临床^[5-6]。肝脏具有特殊肝动脉、门静脉双重供血,了解TACE术前血流特点可为肝癌患者预后评估提供参考依据。范晓华等^[7]研究报道,肝细胞癌患者于数字减影血管造影引导下行TACE后通过超声造影进行疗效评估价值较高,其中达峰时间和增强速率预测价值最优,能够作为预测疗效的辅助影像学方法之一。随着CT技术不断发展、完善,螺旋CT灌注成像观察肿瘤血供受到广泛关注。有研究报道,CT定量参数在评估肝癌病理分化程度、治疗效果等方面优势较为突出,推测其有可能用于TACE治疗的肝癌患者预后评估^[8]。本研究旨在探讨术前CT定量参数与TACE术后肝癌患者预后的相关性,并构建预后预测列线图模型,以期早期评估经TACE治疗的肝癌患者预后不良的风险。

1 资料与方法

1.1 一般资料

选择2020年5月至2022年5月于濮阳市第五

人民医院医学影像科行TACE治疗的120例肝癌患者为研究对象。其中男82例,女38例;年龄40~65(52.36 ± 8.25)岁。病例纳入标准:(1)经穿刺病理活检确诊为肝癌;(2)均行TACE治疗;(3)患者的认知、言语、沟通能力正常,依从性良好;(4)自愿签署相关研究知情同意书。排除标准:(1)伴腹水、严重黄疸或其他系统恶性肿瘤;(2)入组前接受免疫、消融或其他抗肝癌治疗;(3)对CT扫描相关碘试剂过敏;(4)预计生存时间 < 3 个月。本研究获得濮阳市第五人民医院医学伦理委员会审核批准。

1.2 螺旋CT平扫及灌注成像扫描

TACE治疗前完善螺旋CT平扫及灌注成像扫描:患者取仰卧位,平稳呼吸后使用GE Optima680型64排128层螺旋CT机(北京航卫通用电器医疗系统有限公司)行肝脏平扫,确定肿瘤病灶位置后避开坏死区选择感兴趣区(region of interest, ROI)作为灌注扫描层面,动态扫描层面覆盖病灶组织、门静脉,扫描参数:管电压、电流分别为100 kV、200 mA,层厚5 mm,矩阵 512×512 ,以 $4 \text{ mL} \cdot \text{s}^{-1}$ 速率经肘静脉团注碘对比剂($1.0 \text{ mL} \cdot \text{kg}^{-1}$),延迟8 s行动态扫描。将灌注成像扫描图像传送至工作站,应用Advantage Workstation上的perfusion 4D软件分析扫描图像并得到灌注参数图,在灌注参数图上选择ROI,测量各部分ROI CT值,生成对应时间-密度曲线,读取灌注参数,包括肝血流量(hepatic blood flow, HBF)、肝动脉灌注量(hepatic artery perfusion

volume,HAP)、门静脉灌注量(portal vein perfusion volume,PVP)、肝动脉灌注指数(hepatic artery perfusion index,HAI)、平均通过时间(mean transit time,MTT)。

1.3 临床资料收集及病例分组

收集入组患者的临床资料,包括性别、年龄、体质质量指数(body mass index,BMI)、吸烟史、酗酒史、TNM分期、肿瘤最大径、肿瘤数目、包膜是否完整、白蛋白、血小板、总胆红素、白细胞计数、丙氨酸氨基转移酶(alanine aminotransferase,ALT)、天冬氨酸氨基转移酶(aspartate aminotransferase,AST)、甲胎蛋白(alpha-fetoprotein,AFP)。随访至2023年5月,病死患者数据收集至末次随访,将死亡、复发、因严重并发症再次入院的肝癌患者纳入预后不良组($n=30$),随访期间无复发、无严重并发症的患者纳入预后良好组($n=90$)。

1.4 统计学处理

应用SPSS 26.0统计学软件、R软件进行数据统计与分析。计量资料以均数±标准差($\bar{x} \pm s$)表示,2组间比较采用 t 检验;计数资料以例数和百分率表示,2组间比较采用 χ^2 检验;采用logistic多因素回归分析影响经TACE治疗肝癌患者预后的危险因素;应用R软件构建经TACE治疗肝癌患者预后预测列线图模型,应用rms程序包和Bootstrap内部验证法对模型进行验证。检验水准 $\alpha=0.05$ 。

2 结果

2.1 预后良好组与预后不良组患者的临床资料比较

预后不良组患者TNM分期Ⅲ~Ⅳ期占比、包膜不完整占比及AFP、HBF、HAP、HAI水平显著高于预后良好组,MTT显著短于预后良好组,差异有统计学意义($P<0.05$);预后不良组与预后良好组患者的性别构成、年龄、BMI、吸烟史占比、肿瘤最大径 $>5\text{ cm}$ 占比、肿瘤数目 >1 个占比、白蛋白水平、血小板计数、总胆红素水平、ALT水平、AST水平、PVP比较差异无统计学意义($P>0.05$)。结果见表1。

2.2 影响经TACE治疗肝癌患者预后的危险因素

将TNM分期Ⅲ~Ⅳ期、包膜不完整、AFP、HBF、HAP、HAI、MTT作为自变量(X),预后作为因变量(Y)进行logistic多因素回归分析,结果显示,包膜不完整[比值比(odds ratio,OR)=2.202,95%置信区间(confidence interval,CI):1.884~2.880, $P=0.000$]、AFP水平高(OR=2.187,95%CI:1.818~2.787, $P=0.000$)、HBF高(OR=2.177,95%CI:1.859~2.862, $P=0.000$)、HAP高(OR=2.192,95%CI:1.907~2.909, $P=0.000$)、HAI高(OR=

2.212,95%CI:1.926~2.816, $P=0.000$)、MTT短(OR=2.208,95%CI:1.927~2.954, $P=0.000$)是影响经TACE治疗肝癌患者预后的危险因素。结果见表2。

表1 预后良好组与预后不良组患者的临床资料比较

Tab.1 Comparison of clinical data of patients between the good prognosis group and poor prognosis group				
临床资料	预后良好组 ($n=90$)	预后不良组 ($n=30$)	t/χ^2	P
性别				
男/例(%)	62(68.89)	20(66.67)	0.051	0.821
女/例(%)	28(31.11)	10(33.33)		
年龄/岁	52.13±8.15	52.47±8.26	0.197	0.844
BMI/($\text{kg}\cdot\text{m}^{-2}$)	22.26±2.02	22.50±2.09	0.559	0.577
吸烟史/例(%)	50(55.56)	18(60.00)	0.181	0.671
酗酒史/例(%)	60(66.67)	22(73.33)	0.462	0.497
TNM分期				
I~II期/例(%)	44(48.89)	8(26.67)	4.525	0.033
III~IV期/例(%)	46(51.11)	22(73.33)		
肿瘤最大径 $>5\text{ cm}$ /例(%)	45(50.00)	17(56.67)	0.400	0.527
肿瘤数目 >1 个/例(%)	40(44.44)	14(46.67)	0.045	0.832
包膜不完整/例(%)	27(30.00)	20(66.67)	12.696	0.000
白蛋白/($\text{g}\cdot\text{L}^{-1}$)	39.25±2.31	38.82±2.28	0.886	0.378
血小板/($\times 10^9\text{ L}^{-1}$)	111.45±1.90	112.02±2.06	1.393	0.166
总胆红素/($\mu\text{mol}\cdot\text{L}^{-1}$)	20.31±2.54	21.20±2.60	1.652	0.101
白细胞计数/($\times 10^9\text{ L}^{-1}$)	13.36±2.05	13.80±2.09	1.013	0.313
ALT/($\text{U}\cdot\text{L}^{-1}$)	80.25±3.51	81.03±3.40	1.062	0.290
AST/($\text{U}\cdot\text{L}^{-1}$)	76.97±1.25	77.32±1.38	1.294	0.198
AFP/($\mu\text{g}\cdot\text{L}^{-1}$)	372.16±10.07	430.25±12.25	25.880	0.000
HBF/($\text{mL}\cdot\text{min}^{-1}\cdot 100\text{ mL}^{-1}$)	99.12±14.10	156.25±23.20	15.413	0.000
HAP/($\text{mL}\cdot\text{min}^{-1}\cdot 100\text{ mL}^{-1}$)	45.05±5.02	95.26±7.65	40.114	0.000
PVP/($\text{mL}\cdot\text{min}^{-1}\cdot 100\text{ mL}^{-1}$)	31.02±4.26	30.28±4.19	0.827	0.410
HAI/%	24.80±3.27	60.25±6.45	39.320	0.000
MTT/s	10.35±2.20	7.25±1.25	7.321	0.000

表2 影响经TACE治疗肝癌患者预后的危险因素 logistic 多因素回归分析

Tab.2 Logistic multivariate regression analysis of risk factors affecting prognosis of liver cancer patients treated with TACE							
因素	β	SE	Wald χ^2	P	OR	95% CI	
						下限	上限
包膜不完整	0.529	0.617	6.164	0.000	2.202	1.884	2.880
AFP水平高	0.542	0.606	6.137	0.000	2.187	1.818	2.787
HBF高	0.604	0.592	6.227	0.000	2.177	1.859	2.862
HAP高	0.593	0.599	5.997	0.000	2.192	1.907	2.909
HAI高	0.612	0.587	6.106	0.000	2.212	1.926	2.816
MTT短	0.620	0.585	6.092	0.000	2.208	1.927	2.954

2.3 经TACE治疗肝癌患者预后预测列线图模型及验证

基于HBF、HAP、HAI、MTT构建经TACE治疗肝癌患者预后预测列线图模型(见图1)。Calibration验证结果显示实测值与预测值结果基本一致,表明该模型预测性能良好,结果见图2。Bootstrap内部验证法结果显示,C-index为0.908(95%CI:0.787~0.968),表明该模型区分度、准确度均较好,结果见图3。

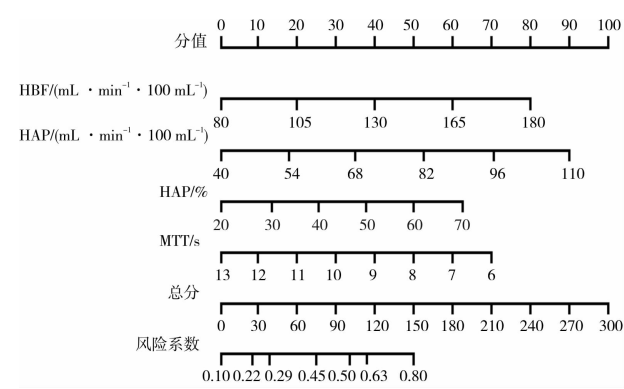


图 1 经 TACE 治疗肝癌患者预后预测列线图模型

Fig.1 Prognostic nomogram model of liver cancer patients treated by TACE

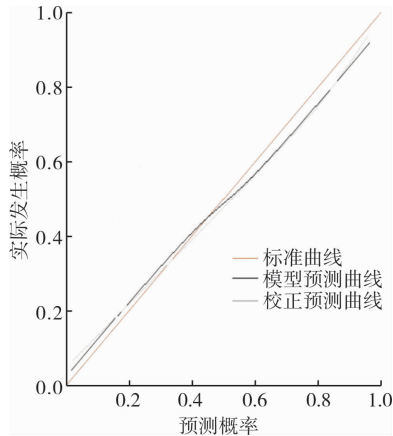


图 2 Calibration 验证经 TACE 治疗肝癌患者预后预测列线图模型

Fig.2 Calibration for prognostic prediction of patients with hepatocellular carcinoma treated by TACE

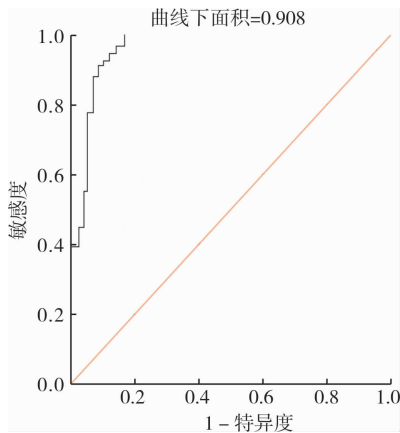


图 3 Bootstrap 内部验证法验证经 TACE 治疗肝癌患者预后预测列线图模型 ROC 曲线图

Fig.3 Bootstrap internal validation validated the ROC curve of the TACE treatment for liver cancer patients

3 讨论

TACE 是临床公认治疗不能手术切除的中晚期

肝癌患者的首选方法,但术后肿瘤复发一直是临床重点关注的问题^[9]。血管生长是肿瘤进展的关键环节,新生血管与邻近组织血管易于在肿瘤细胞活跃期建立侧支循环,病灶 ROI 血流灌注增加,TACE 通过栓塞肝肿瘤病灶血供,减少血流量后使肿瘤细胞发生缺血缺氧、坏死,评估肝癌患者肿瘤血供特点有望评估患者预后^[10-11]。螺旋 CT 灌注成像基于肝脏双重供血特点,定量检测病灶血供以评估血流动力学特点,提供肿瘤生物学行为信息,有望成为判断预后的依据^[12]。

本研究结果显示,与预后良好组比较,预后不良组患者的 HBF、HAP、HAI 较高,MTT 较短。肝癌病理改变主要是肝细胞弥漫性变性坏死、结缔组织增生,此时肝小叶结构、血液循环途径被改建,广泛侧支循环形成后导致门静脉血供减少,因肝脏双重供血的特点,门静脉灌注不足由肝动脉灌注增加补偿,即 HBF 升高^[13-14];HAP、HAI 为肝动脉血供指数,肝肿瘤病灶主要由动脉供血,HAP、HAI 升高提示肿瘤细胞浸润程度较深,病灶已出现形态学改变而被检出,出现此变化趋势可能与病变组织导致血管扭曲或异性型改变有关^[15];肝癌发生后,病灶组织血管管径、通透性显著增加,血供更加畅通,即表现为 MTT 缩短^[16]。本研究将 HBF、HAP、HAI、MTT 纳入 logistic 多因素回归分析发现,HBF、HAP、HAI、MTT 均为影响经 TACE 治疗肝癌患者预后的危险因素,提示临床可基于 CT 定量参数探讨降低肝癌 TACE 术后复发风险的方案以提高患者生存率。除 CT 定量参数外,本研究 logistic 多因素回归分析结果亦显示,包膜不完整、AFP 水平高是经 TACE 治疗肝癌患者预后不良的独立危险因素,分析原因在于:(1)肝癌包膜主要由扩张的肝血窦、纤维结缔组织混合组成,完整的包膜可阻止肿瘤细胞浸润、转移,侧支循环形成概率较低,包膜完整性被破坏后,肿瘤易透过包膜进入周围组织,侵袭能力、转移能力均较强,不利于预后^[17-18];(2)在免疫系统中,AFP 可通过改变 CD4⁺/CD8⁺T 淋巴细胞亚群比例诱导淋巴细胞死亡,降低机体免疫功能,而免疫功能低下可促进肿瘤复发、转移,即 AFP 水平越高,肝癌 TACE 术后复发风险越大^[19]。

列线图基于个体预测变量的数值计算总分,根据总分评估某事件发生风险或生存概率。有研究报道,基于淋巴细胞与血小板评分评估列线图模型预测肝细胞癌肝切除术后预后的效能,结果显示该模型拟合度较高,预测效能良好[C-index:0.732(95% CI:0.691 ~ 0.774)]^[20]。本研究基于 logistic 多因素回归分析筛选出的 CT 定量参数建立经 TACE 治

疗肝癌患者预后预测列线图模型, Calibration 验证结果显示,实测值与预测值结果基本一致,表明该模型预测性能良好; C-index 为 0.908 (95% CI: 0.787~0.968),提示该模型区分度及准确度较好。

4 结论

包膜不完整、AFP 水平高、HBF 高、HAP 高、HAI 高、MTT 低是 TACE 后肝癌患者预后不良的独立危险因素,基于上述 CT 定量参数构建的经 TACE 治疗肝癌患者预后列线图模型预测效能较高。本研究为单中心研究、选取样本量有限,可能降低检验效能,后续需进一步扩大样本量、开展多中心试验以提高本研究相关结论论证强度。

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