

·论著·

脂肪变性供肝用于肝癌肝移植的预后及影响因素多中心研究

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【摘要】 目的 探讨脂肪变性供肝用于肝癌肝移植的预后及影响因素。**方法** 采用回顾性队列研究方法。收集2015年1月至2019年12月2家医学中心收治的152对[树兰(杭州)医院89对、浙江大学医学院附属第一医院63对]脂肪变性供肝用于肝癌肝移植供者和受者的临床病理资料;152例供者,男131例,女21例;年龄为(48±12)岁,供肝轻度脂肪变性130例、中度脂肪变性22例。152例受者,男138例,女14例;年龄为(52±9)岁。观察指标:(1)受者随访、总生存和肿瘤无复发生存情况。(2)受者总生存和肿瘤无复发生存影响因素分析。(3)受者总生存和肿瘤无复发生存列线图预测模型构建及评价。采用门诊和电话方式进行随访,了解受者生存和肿瘤复发情况。随访时间截至2020年12月。正态分布的计量资料以 $\bar{x} \pm s$ 表示,偏态分布的计量资料以 $M(IQR)$ 表示。计数资料以绝对数表示。采用Kaplan-Meier法计算生存率和绘制生存曲线,采用Log-Rank检验进行生存分析。单因素及多因素分析采用COX回归模型。将独立危险因素引入R 3.6.2软件,构建列线图预测模型,绘制受试者工作特征曲线(ROC)并以曲线下面积(AUC)和校准曲线评价模型准确度与区分度。**结果** (1)受者随访、总生存和肿瘤无复发生存情况:152例脂肪变性供肝用于肝癌肝移植受者均获得随访,随访时间为45.8(27.6)个月。随访期间,152例受者总生存时间为36.5(32.3)个月,肿瘤无复发生存时间为30.4(34.6)个月,1、3年总生存率和肿瘤无复发生存率分别为73.4%、55.8%和62.2%、43.4%。(2)受者总生存和肿瘤无复发生存影响因素分析。单因素分析结果显示:供肝冷缺血时间、供肝热缺血时间、移植受者体重比率(GRWR)、ABO血型相容情况、受者体质量指数(BMI)、受者肿瘤长径、受者肿瘤数目、受者肿瘤分化程度、受者术前甲胎蛋白(AFP)是影响受者总生存的相关因素(风险比=6.26, 1.90, 2.47, 4.08, 0.55, 5.16, 3.62, 5.28, 2.65, 95%可信区间为3.01~13.03, 1.07~3.38, 1.36~4.49, 2.07~8.03, 0.31~0.98, 2.56~10.42, 1.95~6.72, 1.60~17.42, 1.48~5.01, $P<0.05$)。供肝冷缺血时间、GRWR、ABO血型相容情况、受者肿瘤长径、受者肿瘤数目、受者肿瘤分化程度、受者术前AFP是影响受者肿瘤无复发生存的相关因素(风险比=4.24, 2.53, 4.05, 3.39, 3.10, 5.19, 2.63, 95%可信区间为2.50~7.21, 1.54~4.17, 2.12~7.72, 2.04~5.62, 1.91~5.03, 2.04~13.18, 1.61~4.30, $P<0.05$)。多因素分析结果显示:供肝冷缺血时间 ≥ 8 h、GRWR $\geq 2.5\%$ 、受者肿瘤长径 ≥ 8 cm、受者术前AFP ≥ 400 $\mu\text{g/L}$ 是影响受者总生存的独立危险因素(风险比=4.21, 2.58, 4.10, 2.27, 95%可信区间为1.98~8.96, 1.24~5.35, 1.35~12.43, 1.13~4.56, $P<0.05$)。供肝冷缺血时间 ≥ 8 h、GRWR $\geq 2.5\%$ 、受者肿瘤长径 ≥ 8 cm、受者肿瘤数目 ≥ 3 个、受者术前AFP ≥ 400 $\mu\text{g/L}$ 是影响受者肿瘤无复发生存的独立危险因素(风险比=3.37, 2.63, 2.42, 2.12, 2.22, 95%可信区间为1.70~6.67, 1.40~4.96, 1.04~5.66, 1.08~4.18, 1.26~3.90, $P<0.05$)。(3)受者总生存和肿瘤无复发生存列线图预测模型构建及评价。纳入供肝冷缺血时间、GRWR、受者肿瘤长径、受者术前AFP构建受者总生存列线图预测模型;纳入供肝冷缺血时间、GRWR、受者肿瘤长径、受者肿瘤数目、

DOI: 10.3760/cma.j.cn115610-20220209-00072

收稿日期 2022-02-09

引用本文:杨梦凡,王睿,潘斌华,等.脂肪变性供肝用于肝癌肝移植的预后及影响因素多中心研究[J].中华消化外科杂志,2022,21(2):237-248. DOI: 10.3760/cma.j.cn115610-20220209-00072.



受者术前 AFP 构建受者肿瘤无复发生存列线图预测模型。ROC 显示:受者总生存列线图预测模型 AUC=0.84(95% 可信区间为 0.76~0.92, $P<0.05$), 诊断最佳临界值为 7.3, 特异度、灵敏度分别为 87.6%、70.0%。受者肿瘤无复发生存列线图预测模型 AUC=0.79(95% 可信区间为 0.71~0.87, $P<0.05$), 诊断最佳临界值为 5.8, 特异度、灵敏度分别为 97.4%、52.5%。校准曲线显示:列线图预测模型对受者总生存和肿瘤无复发生存高危人群具有良好区分度。**结论** 供肝冷缺血时间 ≥ 8 h、GRWR $\geq 2.5\%$ 、受者肿瘤长径 ≥ 8 cm、受者术前 AFP ≥ 400 $\mu\text{g/L}$ 是影响脂肪变性供肝用于肝癌肝移植受者总生存的独立危险因素;供肝冷缺血时间 ≥ 8 h、GRWR $\geq 2.5\%$ 、受者肿瘤长径 ≥ 8 cm、受者肿瘤数目 ≥ 3 个、受者术前 AFP ≥ 400 $\mu\text{g/L}$ 是影响脂肪变性供肝用于肝癌肝移植受者肿瘤无复发生存的独立危险因素。

【关键词】 肝肿瘤; 肝移植; 脂肪变性供肝; 预后; 肿瘤复发; 列线图

基金项目:国家重点研发计划(2021YFA1100500);国家自然科学基金(81702858、81930016、92159202);浙江省科技厅重点研发计划(2019C03050、2022C03108);浙江省医药卫生科技计划项目(2016KYB087、2018KY375)

Prognosis and influencing factors of liver transplantation for hepatocellular carcinoma using steatotic donor liver: a multicenter study

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【Abstract】 **Objective** To investigate the prognosis and influencing factors of liver transplantation (LT) for hepatocellular carcinoma (HCC) using steatotic donor liver. **Methods** The retrospective cohort study was conducted. The clinicopathological data of 152 pairs of donors and the corresponding recipients undergoing LT for HCC in the two medical centers [89 pairs in Shulan (Hangzhou) Hospital and 63 pairs in the First Affiliated Hospital of Zhejiang University School of Medicine] from January 2015 to December 2019 were collected. Of 152 donors, there were 131 males and 21 females, aged (48 \pm 12)years, and there were 130 cases with liver mild steatosis and 22 cases with liver moderate steatosis. Of 152 recipients, there were 138 males and 14 females, aged (52 \pm 9)years. Observation indicators: (1) follow-up, overall survival and tumor recurrence free survival of recipients; (2) influencing factors for overall survival and tumor recurrence free survival of recipients; (3) construction and validation of nomogram prediction model for overall survival and tumor recurrence free survival of recipients. Follow-up was conducted using outpatient examination and telephone interview to detect survival and tumor recurrence of recipients up to December 2020. Measurement data with normal distribution were represented as $Mean\pm SD$, and measurement data with skewed distribution were represented as $M(IQR)$. Count data were described as absolute numbers. The Kaplan-Meier method was used to calculate the survival time and draw survival curve, and the Log-Rank test was used for survival analysis. The COX regression model was used for univariate and multivariate analysis. The independent risk factors were brought into the R 3.6.2 software to construct nomogram prediction model and draw the receiver operating characteristic (ROC) curve. The accuracy and discrimination of the nomogram prediction model were evaluated using the area under curve (AUC) and the calibration curve. **Results** (1) Follow-up, overall survival and tumor recurrence free survival of recipients. All the 152 recipients undergoing LT for HCC using steatotic donor liver were followed up for 45.8(27.6)months, with the overall survival time and tumor recurrence free survival time of 36.5(32.3)months and 30.4(34.6)months. The 1-year, 3-year overall survival rates and tumor recurrence free rates of the 152 recipients were 73.4%, 55.8% and 62.2%, 43.4%, respectively. (2) Influencing factors for overall survival and tumor recurrence free survival of recipients. Results of univariate analysis showed that the donor liver cold ischemia time (CIT), the donor liver warm ischemia time (WIT), graft-to-recipient weight ratio (GRWR), ABO compatibility, recipient body mass index (BMI), recipient tumor diameter, recipient tumor number, recipient tumor differentiation degree, recipient preoperative alpha fetoprotein (AFP) were related factors influencing the overall survival of recipients ($hazard\ ratio=6.26, 1.90, 2.47, 4.08, 0.55, 5.16,$

3.62, 5.28, 2.65, 95% confidence interval as 3.01–13.03, 1.07–3.38, 1.36–4.49, 2.07–8.03, 0.31–0.98, 2.56–10.42, 1.95–6.72, 1.60–17.42, 1.48–5.01, $P<0.05$) and the donor liver CIT, GRWR, ABO compatibility, recipient tumor diameter, recipient tumor number, recipient tumor differentiation degree, recipient preoperative AFP were related factors influencing the tumor recurrence free survival of recipients (hazard ratio=4.24, 2.53, 4.05, 3.39, 3.10, 5.19, 2.63, 95% confidence interval as 2.50–7.21, 1.54–4.17, 2.12–7.72, 2.04–5.62, 1.91–5.03, 2.04–13.18, 1.61–4.30, $P<0.05$). Results of multivariate analysis showed that donor liver CIT ≥ 8 hours, GRWR $\geq 2.5\%$, recipient tumor diameter ≥ 8 cm and recipient preoperative AFP ≥ 400 $\mu\text{g/L}$ were independent risk factors influencing the overall survival of recipients (hazard ratio=4.21, 2.58, 4.10, 2.27, 95% confidence interval as 1.98–8.96, 1.24–5.35, 1.35–12.43, 1.13–4.56, $P<0.05$) and donor liver CIT ≥ 8 hours, GRWR $\geq 2.5\%$, recipient tumor diameter ≥ 8 cm, recipient tumor number ≥ 3 and recipient preoperative AFP ≥ 400 $\mu\text{g/L}$ were independent risk factors influencing the tumor recurrence free survival of recipients (hazard ratio=3.37, 2.63, 2.42, 2.12, 2.22, 95% confidence interval as 1.70–6.67, 1.40–4.96, 1.04–5.66, 1.08–4.18, 1.26–3.90, $P<0.05$). (3) Construction and validation of nomogram prediction model for overall survival and tumor recurrence free survival of recipients. The donor liver CIT, GRWR, recipient tumor diameter, recipient preoperative AFP were used to construct nomogram prediction model for overall survival of recipients and the donor liver CIT, GRWR, recipient tumor diameter, recipient tumor number, recipient preoperative AFP were used to construct nomogram prediction model for tumor recurrence free survival of recipients. The ROC curve showed that the AUC of the nomogram prediction model for overall survival of recipients was 0.84 (95% confidence interval as 0.76–0.92, $P<0.05$), with the optimal diagnostic value as 7.3 and the specificity and sensitivity as 87.6% and 70.0%. The AUC of the nomogram prediction model for tumor recurrence free survival of recipients was 0.79 (95% confidence interval as 0.71–0.87, $P<0.05$), with the optimal diagnostic value as 5.8 and the specificity and sensitivity as 97.4% and 52.5%. The calibration curve showed that the nomogram prediction model had good distinction for high risk recipients in overall survival and tumor recurrence free survival. **Conclusion** Donor liver CIT ≥ 8 hours, GRWR $\geq 2.5\%$, recipient tumor diameter ≥ 8 cm and recipient preoperative AFP ≥ 400 $\mu\text{g/L}$ are independent risk factors influencing the overall survival of recipients who underwent LT for HCC using steatotic donor liver and donor liver CIT ≥ 8 hours, GRWR $\geq 2.5\%$, recipient tumor diameter ≥ 8 cm, recipient tumor number ≥ 3 and recipient preoperative AFP ≥ 400 $\mu\text{g/L}$ are independent risk factors influencing the tumor recurrence free survival of recipients.

【Key words】 Liver neoplasms; Liver transplantation; Steatotic donor liver; Prognosis; Tumor recurrence; Nomogram

Fund programs: National Key Research and Development Program of China (2021YFA1100500); National Natural Science Foundation of China (81702858, 81930016, 92159202); Key Research&Development Plan of Zhejiang Province (2019C03050, 2022C03108); Medicine and Health Care Project of Zhejiang Provincial Science and Technology Plan (2016KYB087, 2018KY375)

肝细胞癌(以下简称肝癌)是我国常见消化系统恶性肿瘤之一,每年死亡患者>30万,占全世界肝癌死亡患者的50%^[1-2]。肝移植是治疗肝癌的有效手段,2019年我国共施行肝移植6 170例,其中肝癌肝移植2 133例,占34.57%^[3]。肝癌肝移植适应证标准不断改进,使更多肝癌患者受益^[4-6]。目前肝移植面临供肝短缺瓶颈难题,但脂肪变性供肝在内的边缘性供肝临床探索应用可有效解决供肝来源问题^[7-9]。脂肪变性供肝是影响肝移植后受者生存的重要危险因素,肝脏脂肪变性程度是影响肝癌肝切除术后肿瘤复发的重要因素^[10-12]。本研究回顾性分析2015年1月至2019年12月2家医学中心收治的152对[树兰(杭州)医院89对、浙江大学

医学院附属第一医院63对]脂肪变性供肝用于肝癌肝移植供者和受者的临床病理资料,探讨脂肪变性供肝用于肝癌肝移植的预后及影响因素。

资料与方法

一、一般资料

采用回顾性队列研究方法。收集152对肝癌肝移植供者和受者的临床病理资料;152例供者,男131例,女21例;年龄为(48 \pm 12)岁,供肝轻度脂肪变性130例、中度脂肪变性22例。152例受者,男138例,女14例;年龄为(52 \pm 9)岁。本研究通过中国肝移植注册科学委员会审批,批号为20200073。

二、纳入标准和排除标准

纳入标准:(1)肝癌肝移植。(2)公民逝世后器官捐献。(3)供肝组织病理学检查结果示大泡型脂肪变性程度为5%~60%。(4)临床病理资料完整。

排除标准:(1)良性肝脏疾病肝移植。(2)术后组织病理学检查证实为胆管细胞癌或混合型肝癌。(3)儿童肝移植。(4)劈裂式肝移植。(5)联合器官移植。(6)合并其他恶性肿瘤病史。(7)临床病理资料缺失。

三、观察指标和评价标准

观察指标:(1)受者随访、总生存和肿瘤无复发生存情况包括获得随访的受者例数,随访时间,总生存时间,肿瘤无复发生存时间,1、3年总生存率和肿瘤无复发生存率。(2)受者总生存和肿瘤无复发生存影响因素分析包括供者性别、供者年龄、供者BMI、供者来源、供肝大泡型脂肪变性程度、供肝冷缺血时间、供肝热缺血时间、移植物受者体重比率(graft to recipient weight ratio, GRWR)、ABO血型相容情况、受者性别、受者年龄、受者BMI、受者终末期肝病模型(model for end-stage liver disease, MELD)评分、受者肝功能Child-Pugh评分、受者肿瘤长径、受者肿瘤数目、受者肿瘤分化程度、受者术前AFP。(3)受者总生存和肿瘤无复发生存列线图预测模型构建及评价。

评价指标:(1)供肝脂肪变性程度依据《中国肝移植供肝获取技术规范(2019版)》^[13]。(2)肿瘤复发定义为肝移植后受者肿瘤标志物(AFP或异常凝血酶原PIVKA-II)>正常值上限并持续升高或经影像学检查发现肿瘤病灶。(3)受者生存时间定义为手术时间至随访截止时间。

四、随访

采用门诊和电话方式进行随访,了解受者生存和肿瘤复发情况。随访时间截至2020年12月。

五、统计学分析

应用SPSS 24.0统计软件进行分析。正态分布的计量资料以 $\bar{x} \pm s$ 表示,偏态分布的计量资料以 $M(IQR)$ 表示。计数资料以绝对数表示。采用Kaplan-Meier法计算生存率和绘制生存曲线,采用Log-Rank检验进行生存分析。单因素及多因素分析采用COX回归模型。将独立危险因素引入R 3.6.2软件,构建列线图预测模型。绘制受试者工作特征曲线(receiver operating characteristic curve, ROC)并以曲线下面积(area under curve, AUC)和校准曲线评价模型准确性与区分度。 $P < 0.05$ 为差异有统计学意义。

结 果

一、受者随访、总生存和肿瘤无复发生存情况

152例脂肪变性供肝用于肝癌肝移植受者均获得随访,随访时间为45.8(27.6)个月。随访期间,152例受者总生存时间为36.5(32.3)个月,肿瘤无复发生存时间为30.4(34.6)个月,1、3年总生存率和肿瘤无复发生存率分别为73.4%、55.8%和62.2%、43.4%。见图1,2。

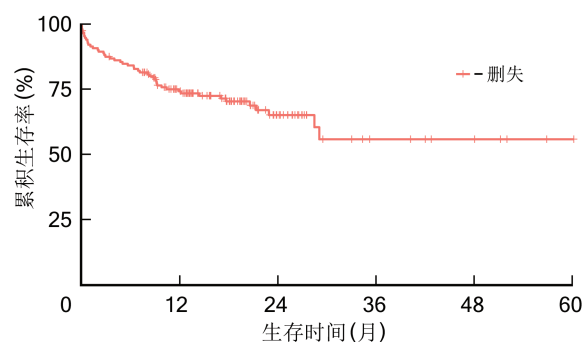


图1 152例脂肪变性供肝用于肝癌肝移植受者的总生存曲线

Figure 1 Overall survival curve of 152 hepatocellular carcinoma patients undergoing liver transplantation with steatotic donor liver

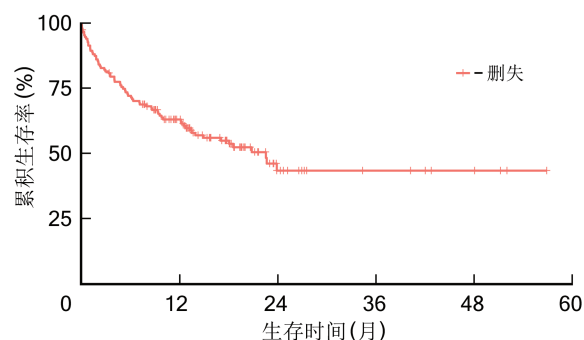


图2 152例脂肪变性供肝用于肝癌肝移植受者的肿瘤无复发生存曲线

Figure 2 Tumor recurrence free survival curve of 152 hepatocellular carcinoma patients undergoing liver transplantation with steatotic donor liver

二、受者总生存和肿瘤无复发生存影响因素分析

单因素分析结果显示:供肝冷缺血时间、供肝热缺血时间、GRWR、ABO血型相容情况、受者BMI、受者肿瘤长径、受者肿瘤数目、受者肿瘤分化程度、受者术前AFP是影响受者总生存的相关因素($P < 0.05$)。供者性别、供者年龄、供者BMI、供者来源、供肝大泡型脂肪变性程度、受者性别、受者年龄、受者MELD评分、受者肝功能Child-Pugh评分不是影响受者总生存的相关因素($P > 0.05$)。见表1。

表 1 影响 152 例脂肪变性供肝用于肝癌肝移植受者总生存的单因素分析

Table 1 Univariate analysis of overall survival in 152 hepatocellular carcinoma patients undergoing liver transplantation with steatotic donor liver

临床病理因素	赋值	例数	3 年总生存率(%)	风险比(95% 可信区间)	P 值
供者性别					
男	1	131	59.6	0.89(0.38~2.10)	0.792
女	0	21	64.8		
供者年龄(岁)					
18~50	0	82	51.5	1.54(0.85~2.80)	0.156
≥50	1	70	51.0		
供者体质量指数(kg/m ²)					
≤23	0	63	69.6	1.41(0.73~2.73)	0.312
>23	1	89	53.2		
供者来源					
脑死亡供者	0	50	60.3	1.36(0.92~2.02)	0.127
心死亡供者	1	102	63.9		
供肝大泡型脂肪变性程度(%)					
5~30	0	130	53.4	1.12(0.50~2.51)	0.777
>30	1	22	63.2		
供肝冷缺血时间(h)					
<8	0	76	79.3	6.26(3.01~13.03)	<0.001
≥8	1	76	33.5		
供肝热缺血时间(min)					
<5	0	93	64.8	1.90(1.07~3.38)	0.030
≥5	1	59	38.3		
移植物受者体重比率(%)					
<2.5	0	95	62.6	2.47(1.36~4.49)	0.003
≥2.5	1	57	53.8		
ABO 血型相容情况					
相容	0	138	59.4	4.08(2.07~8.03)	<0.001
不相容	1	14	19.3		
受者性别					
男	1	138	53.1	0.65(0.20~2.10)	0.475
女	0	14	77.1		
受者年龄(岁)					
<60	0	121	59.3	0.98(0.46~1.96)	0.884
≥60	1	31	42.7		
受者体质量指数(kg/m ²)					
≤23	0	70	55.2	0.55(0.31~0.98)	0.043
>23	1	82	65.5		
受者终末期肝病模型评分(分)					
<30	0	76	55.5	1.13(0.63~2.02)	0.679
≥30	1	76	70.4		
受者肝功能 Child-Pugh 评分(分)					
≤10	0	83	59.1	1.08(0.60~1.95)	0.799
>10	1	69	69.2		
受者肿瘤长径(cm)					
<8	0	81	83.3	5.16(2.56~10.42)	<0.001
≥8	1	71	26.1		

续表1

临床病理因素	赋值	例数	3年总生存率(%)	风险比(95%可信区间)	P值
受者肿瘤数目(个)					
1~2	0	91	77.6	3.62(1.95~6.72)	<0.001
≥3	1	61	30.6		
受者肿瘤分化程度					
高分化 ^a	1	28	59.5	—	—
中分化	2	103	62.0	2.26(0.65~7.88)	0.201
低分化	3	21	34.3	5.28(1.60~17.42)	0.006
受者术前甲胎蛋白(μg/L)					
<400	0	111	60.6	2.65(1.48~5.01)	0.001
≥400	1	41	37.3		

注:^a为多分类变量,采用哑变量分析,该变量设为哑变量;“—”表示此项无

供肝冷缺血时间、GRWR、ABO血型相容情况、受者肿瘤长径、受者肿瘤数目、受者肿瘤分化程度、受者术前AFP是影响受者肿瘤无复发生存的相关因素($P<0.05$)。供者性别、供者年龄、供者BMI、供者来源、供肝大泡型脂肪变性程度、供肝热缺血时间、受者性别、受者年龄、受者BMI、受者MELD评分、受者肝功能Child-Pugh评分不是影响受者肿瘤无复发生存的相关因素($P>0.05$)。见表2。

多因素分析结果显示:供肝冷缺血时间 ≥ 8 h、GRWR $\geq 2.5\%$ 、受者肿瘤长径 ≥ 8 cm、受者术前AFP ≥ 400 μg/L是影响受者总生存的独立危险因素($P<0.05$)。见表3。

供肝冷缺血时间 ≥ 8 h、GRWR $\geq 2.5\%$ 、受者肿瘤长径 ≥ 8 cm、受者肿瘤数目 ≥ 3 个、受者术前AFP ≥ 400 μg/L是影响受者肿瘤无复发生存的独立危险因素($P<0.05$)。见表4。

表2 影响152例脂肪变性供肝用于肝癌肝移植受者肿瘤无复发生存的单因素分析
Table 2 Univariate analysis of tumor recurrence free survival in 152 hepatocellular carcinoma patients undergoing liver transplantation with steatotic donor liver

临床病理因素	赋值	例数	3年肿瘤无复发生存率(%)	风险比(95%可信区间)	P值
供者性别					
男	1	131	46.5	1.16(0.61~2.21)	0.650
女	0	21	34.2		
供者年龄(岁)					
18~50	0	82	38.7	0.74(0.46~1.19)	0.209
≥50	1	70	49.9		
供者体质指数(kg/m ²)					
≤23	0	63	44.5	1.29(0.76~2.17)	0.346
>23	1	89	42.4		
供者来源					
脑死亡	0	50	52.0	1.36(0.98~1.89)	0.104
心死亡	1	102	45.9		
供肝大泡型脂肪变性程度(%)					
5~30	0	130	44.5	1.20(0.63~2.29)	0.577
>30	1	22	34.9		
供肝冷缺血时间(h)					
<8	0	76	59.3	4.24(2.50~7.21)	<0.001
≥8	1	76	34.3		
供肝热缺血时间(min)					
<5	0	93	45.0	1.41(0.87~2.27)	0.165
≥5	1	59	46.0		

续表2

临床病理因素	赋值	例数	3年肿瘤无复发生存率(%)	风险比(95%可信区间)	P值
移植物受者体重比率(%)					
<2.5	0	95	58.7	2.53(1.54~4.17)	<0.001
≥2.5	1	57	34.5		
ABO 血型相容情况					
相容	0	138	47.2	4.05(2.12~7.72)	<0.001
不相容	1	14	15.5		
受者性别					
男	1	138	42.1	0.68(0.27~1.69)	0.404
女	0	14	57.1		
受者年龄(岁)					
<60	0	121	44.6	1.14(0.64~2.01)	0.665
≥60	1	31	39.5		
受者体质量指数(kg/m ²)					
≤23	0	70	36.7	0.56(0.35~0.90)	0.107
>23	1	82	48.4		
受者终末期肝病模型评分(分)					
<30	0	76	37.5	0.90(0.56~1.44)	0.661
≥30	1	76	47.6		
受者肝功能 Child-Pugh评分(分)					
≤10	0	83	43.2	0.70(0.43~1.14)	0.152
>10	1	69	60.8		
受者肿瘤长径(cm)					
<8	0	81	59.7	3.39(2.04~5.62)	<0.001
≥8	1	71	23.4		
受者肿瘤数目(个)					
1~2	0	91	56.3	3.10(1.91~5.03)	<0.001
≥3	1	61	24.5		
受者肿瘤分化程度					
高分化 ^a	1	28	59.5	—	—
中分化	2	103	40.4	2.26(0.86~5.94)	0.109
低分化	3	21	23.6	5.19(2.04~13.18)	0.001
受者术前甲胎蛋白(μg/L)					
<400	0	111	51.4	2.63(1.61~4.30)	<0.001
≥400	1	41	24.1		

注:^a为多分类变量,采用哑变量分析,该变量设为哑变量;“—”表示此项无

三、受者总生存和肿瘤无复发生存列线图预测模型构建及评价

纳入供肝冷缺血时间、GRWR、受者肿瘤长径、受者术前 AFP 构建受者总生存列线图预测模型。见图 3。纳入供肝冷缺血时间、GRWR、受者肿瘤长径、受者肿瘤数目、受者术前 AFP 构建受者肿瘤无复发生存列线图预测模型。见图 4。

ROC 显示:受者总生存列线图预测模型 AUC=0.84(95%CI 为 0.76~0.92, $P=0.009$), 诊断最佳临界值为 7.3, 特异度、灵敏度分别为 87.6%、70.0%。见

图 5。受者肿瘤无复发生存列线图预测模型 AUC=0.79(95%CI 为 0.71~0.87, $P=0.022$), 诊断最佳临界值为 5.8, 特异度、灵敏度分别为 97.4%、52.5%。见图 6。

校准曲线显示:列线图预测模型对受者总生存和肿瘤无复发生存高危人群具有良好区分度。见图 7, 8。

讨 论

一、脂肪变性供肝的临床应用

我国是肝病高发国家,非酒精性脂肪肝和酒精

表 3 影响 152 例脂肪变性供肝用于肝癌肝移植受者总生存的多因素分析

Table 3 Multivariate analysis of overall survival in 152 hepatocellular carcinoma patients undergoing liver transplantation with steatotic donor liver

临床病理因素	赋值	例数	3 年总生存率 (%)	b 值	标准误	Wald 值	风险比(95% 可信区间)	P 值
供肝冷缺血时间(h)								
<8	0	76	79.3					
≥8	1	76	33.5	1.44	0.35	10.59	4.21(1.98~8.96)	<0.001
供肝热缺血时间(min)								
<5	0	93	64.8					
≥5	1	59	38.3	0.16	0.35	0.05	1.17(0.59~2.33)	0.653
移植受体体重比率(%)								
<2.5	0	95	62.6					
≥2.5	1	57	53.8	0.95	0.37	6.69	2.58(1.24~5.35)	0.008
ABO 血型相容情况								
相容	0	138	59.4					
不相容	1	14	19.3	0.39	0.53	0.59	1.48(0.53~4.15)	0.456
受体质量指数(kg/m ²)								
≤23	0	70	55.2					
>23	1	82	65.5	-0.26	0.39	0.29	0.77(0.37~1.70)	0.556
受者肿瘤长径(cm)								
<8	0	81	83.3					
≥8	1	71	26.1	1.41	0.59	5.84	4.10(1.35~12.43)	0.014
受者肿瘤数目(个)								
1~2	0	91	77.6					
≥3	1	61	30.6	0.31	0.54	0.25	1.36(0.47~3.89)	0.570
受者肿瘤分化程度								
高分化 ^a	1	28	59.5	-	-	-	-	-
中分化	2	103	62.0	0.45	0.46	1.06	1.57(0.63~3.88)	0.333
低分化	3	21	34.3	1.22	0.54	2.64	3.39(1.04~11.08)	0.117
受者术前甲胎蛋白(μg/L)								
<400	0	111	60.6					
≥400	1	41	37.3	0.82	0.36	5.23	2.27(1.13~4.56)	0.021

注:^a为多分类变量,采用哑变量分析,该变量设为哑变量;“-”表示此项无

性肝病发病率呈逐年上升趋势^[14-17]。肝移植是治疗终末期肝病的有效措施,但供肝缺乏一直是临床面临的瓶颈问题。公民逝世后器官捐献体系的建立与完善扩大了供肝来源,其中包括脂肪变性供肝在内的边缘性供肝拓展应用成为研究热点^[18-19]。脂肪变性供肝组织病理学表现包括小泡型和大泡型脂肪变性,而大泡型脂肪变性可根据脂肪变性程度分为轻度(5%≤脂肪变性程度<30%、中度(30%≤脂肪变性程度<60%)、重度(脂肪变性程度≥60%)^[13,20]。《中国肝移植供肝获取技术规范(2019版)》建议小泡型及轻度大泡型脂肪变性供肝可常规应用,中度大泡型脂肪变性供肝应慎重选用,避免应用重度大泡型脂肪变性供肝^[13]。有研究结果显示:脂肪变性供肝移植后早期,供肝功能障碍和血

管及胆道并发症发生率相对升高,且脂肪变性供肝是影响受者肿瘤复发的重要因素^[21-23]。

二、影响肝癌肝移植预后的供者因素

GRWR是评价供肝与受者匹配的重要指标,通常认为GRWR需>0.8%,否则移植后易发生小肝综合征^[24-26]。有研究结果显示:GRWR与活体肝移植后他克莫司代谢及肿瘤复发密切相关^[27]。供肝缺血再灌注损伤是公民逝世后器官捐献常见并发症,可导致移植后供肝功能延迟恢复等严重不良反应。《中国肝移植供肝获取技术规范(2019版)》建议供肝冷缺血时间应≤8 h^[13]。美国学者的研究结果显示:对于存在血管侵犯的肝癌肝移植受者,供肝冷缺血时间>10 h将提高受者移植后肿瘤复发率^[28]。脂肪酸是肿瘤细胞重要能量来源,靶向肿瘤细胞脂

表 4 影响 152 例脂肪变性供肝用于肝癌肝移植受者肿瘤无复发生存的多因素分析

Table 4 Multivariate analysis of tumor recurrence free survival in 152 hepatocellular carcinoma patients undergoing liver transplantation with steatotic donor liver

临床病理因素	赋值	例数	3 年肿瘤无复发生存率(%)	b 值	标准误	Wald 值	风险比(95% 可信区间)	P 值
供肝冷缺血时间(h)								
<8	0	76	59.3					
≥8	1	76	22.9	1.22	0.29	11.40	3.37(1.70~6.67)	<0.001
移植受体体重比率(%)								
<2.5	0	95	58.7					
≥2.5	1	57	34.5	0.97	0.28	10.92	2.63(1.40~4.96)	<0.001
ABO 血型相容情况								
相容	0	138	47.2					
不相容	1	14	15.5	0.12	0.42	0.10	1.13(0.64~1.99)	0.689
受者肿瘤长径(cm)								
<8	0	81	59.7					
≥8	1	71	23.4	0.89	0.45	4.41	2.42(1.04~5.66)	0.038
受者肿瘤数目(个)								
1~2	0	91	56.3					
≥3	1	61	24.5	0.75	0.43	4.84	2.12(1.08~4.18)	0.029
受者肿瘤分化程度								
高分化 ^a	1	28	59.5	—	—	—	—	—
中分化	2	103	40.4	0.33	0.40	1.01	1.39(0.73~2.65)	0.322
低分化	3	21	23.6	0.66	0.46	2.65	1.94(0.88~4.28)	0.115
受者术前甲胎蛋白(μg/L)								
<400	0	111	51.4					
≥400	1	41	24.1	0.80	0.29	7.35	2.22(1.26~3.90)	0.006

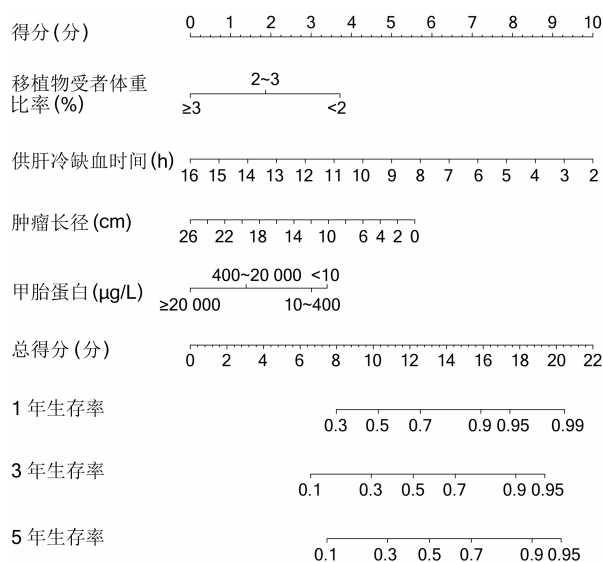
注:^a为多分类变量,采用哑变量分析,该变量设为哑变量;“—”表示此项无

图 3 152 例脂肪变性供肝用于肝癌肝移植受者的总生存列线图

Figure 3 Nomogram for overall survival of 152 hepatocellular carcinoma patients undergoing liver transplantation with steatotic donor liver

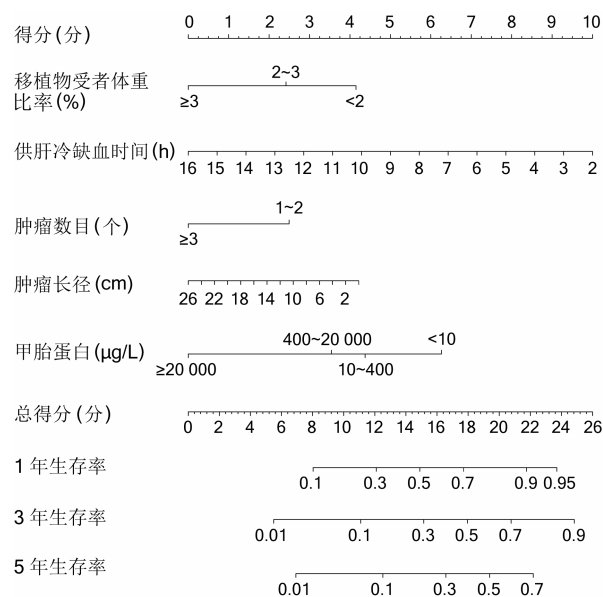


图 4 152 例脂肪变性供肝用于肝癌肝移植受者的肿瘤无复发生存列线图

Figure 4 Nomogram for tumor recurrence free survival of 152 hepatocellular carcinoma patients undergoing liver transplantation with steatotic donor liver

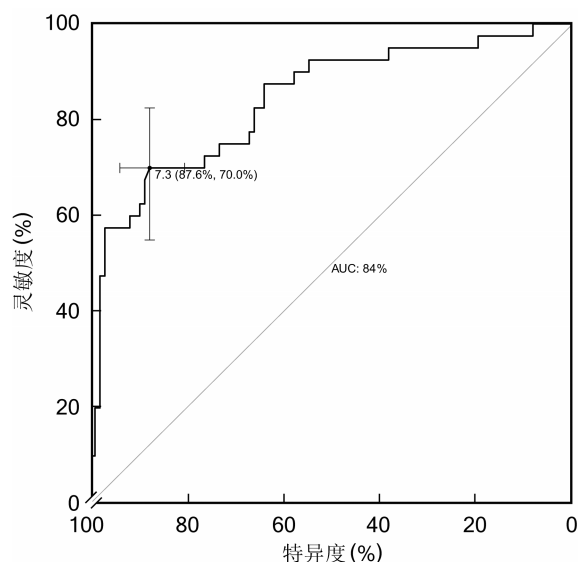


图5 152例脂肪变性供肝用于肝癌肝移植受者总生存列线图预测模型的受试者工作特征曲线

Figure 5 Receiver operating characteristic curve of nomogram prediction model for overall survival of 152 hepatocellular carcinoma patients undergoing liver transplantation with steatotic donor liver

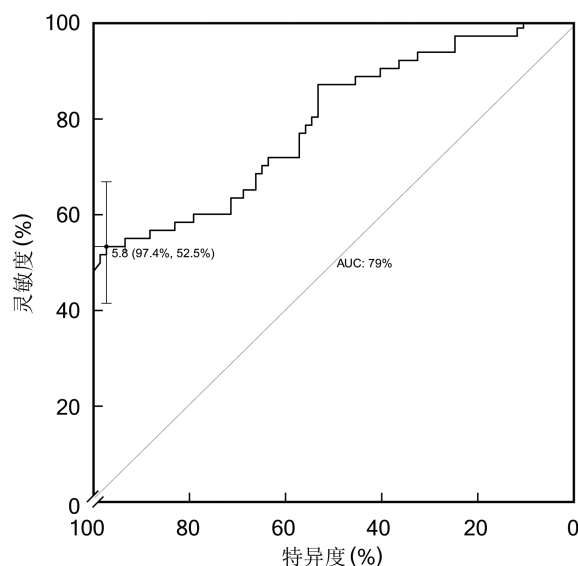


图6 152例脂肪变性供肝用于肝癌肝移植受者肿瘤无复发生存列线图预测模型的受试者工作特征曲线

Figure 6 Receiver operating characteristic curve of nomogram prediction model for tumor recurrence free survival of 152 hepatocellular carcinoma patients undergoing liver transplantation with steatotic donor liver

代谢通路治疗已成为一种新的抗肿瘤策略^[29-31]。有研究结果显示:脂肪变性供肝叠加缺血再灌注损伤会进一步增加移植后肿瘤复发风险^[32-33]。本研究结果显示:供肝冷缺血时间 ≥ 8 h、GRWR ≥ 2.5 是影响受者生存和肿瘤复发的独立危险因素。笔者

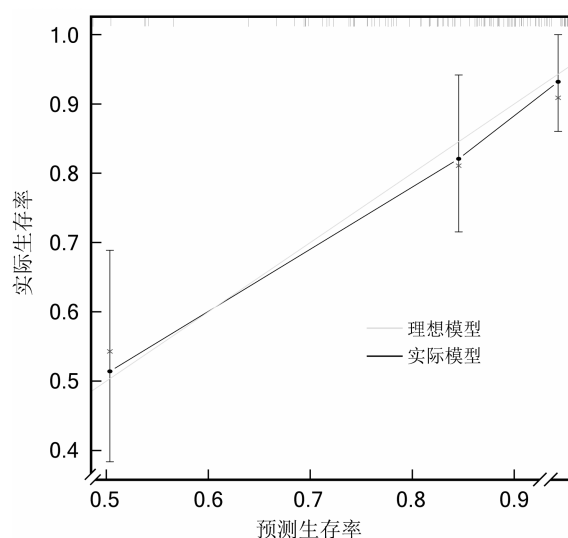


图7 152例脂肪变性供肝用于肝癌肝移植受者总生存列线图预测模型的校准曲线

Figure 7 Calibration curve of nomogram prediction model for overall survival of 152 hepatocellular carcinoma patients undergoing liver transplantation with steatotic donor liver

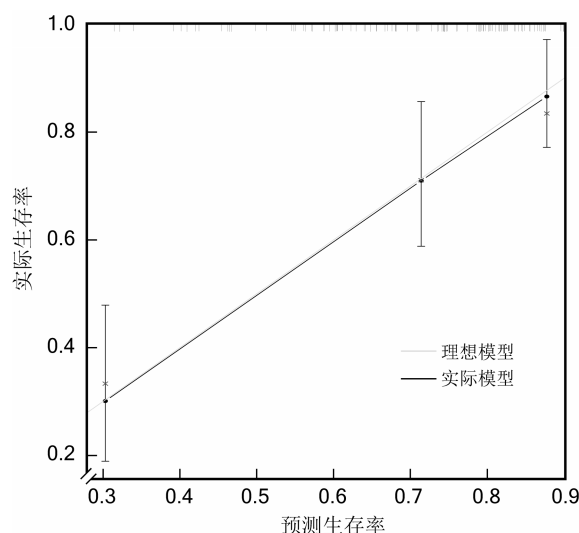


图8 152例脂肪变性供肝用于肝癌肝移植受者肿瘤无复发生存列线图预测模型的校准曲线

Figure 8 Calibration curve of nomogram prediction model for tumor recurrence free survival of 152 hepatocellular carcinoma patients undergoing liver transplantation with steatotic donor liver

认为:对于脂肪变性供肝,应尽量缩短冷缺血时间。近年来兴起的机械灌注技术能够持续为离体器官提供氧气、营养物质,可更好地维护供肝^[34]。而脂肪变性供肝独特的代谢微环境可能为移植后肿瘤复发提供条件,但具体机制需进一步研究证实。

三、影响肝癌肝移植预后的受者因素

以往的研究结果显示:肿瘤生物学参数是选择

合适肝癌肝移植受者和预测预后的重要指标^[35-36]。本研究结果显示:受者肿瘤长径 ≥ 8 cm、受者术前 AFP ≥ 400 $\mu\text{g/L}$ 是影响受者生存的独立危险因素;受者肿瘤长径 ≥ 8 cm、受者肿瘤数目 ≥ 3 个、受者术前 AFP ≥ 400 $\mu\text{g/L}$ 是影响受者肿瘤复发的独立危险因素。

四、肝癌肝移植受者生存和肿瘤复发的预测模型研究

从 1996 年 Mazzaferro 教授提出“米兰标准”到 2008 年郑树森院士创建包含肿瘤生物学特性的肝癌肝移植“杭州标准”,肝癌肝移植受者选择标准一直在突破和进步^[37]。有研究结果显示:根据多因素回归分析得到高危因素构建的列线图预测模型,可直观表现患者发生临床结局的概率,帮助临床医师有效筛选高危患者并给予干预措施^[38-39]。本研究基于多因素分析结果构建受者总生存和肿瘤无复发生存列线图预测模型,AUC 和校准曲线显示:列线图预测模型具有良好的准确度和区分度。

综上,供肝冷缺血时间 ≥ 8 h、GRWR $\geq 2.5\%$ 、受者肿瘤长径 ≥ 8 cm、受者术前 AFP ≥ 400 $\mu\text{g/L}$ 是影响脂肪变性供肝用于肝癌肝移植受者总生存的独立危险因素;供肝冷缺血时间 ≥ 8 h、GRWR $\geq 2.5\%$ 、受者肿瘤长径 ≥ 8 cm、受者肿瘤数目 ≥ 3 个、受者术前 AFP ≥ 400 $\mu\text{g/L}$ 是影响脂肪变性供肝用于肝癌肝移植受者肿瘤无复发生存的独立危险因素。

利益冲突 所有作者均声明不存在利益冲突

作者贡献声明 杨梦凡:研究设计、任务分配、结果总结与评估、文章撰写;王睿、潘斌华、苏仁义、董思依:资料收集与数据分析;徐骁、郑树森、魏绪勇:文章审核

参 考 文 献

- 中国医师协会器官移植医师分会,中华医学会器官移植学分会.中国肝癌肝移植临床实践指南(2018版)[J].临床肝胆病杂志,2019,35(2):275-280. DOI:10.3969/j.issn.1001-5256.2019.02.008.
- Ferlay J, Colombet M, Soerjomataram I, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods[J]. Int J Cancer, 2019, 144(8): 1941-1953. DOI:10.1002/ijc.31937.
- 黄洁夫.中国器官移植发展报告(2019)[M].北京:清华大学出版社,2020.
- 吕少诚,潘冰,李立新,等.不同肝癌肝移植标准受者预后分析[J/CD].中华移植杂志:电子版,2019,13(3):206-209. DOI:10.3877/cma.j.issn.1674-3903.2019.03.009.
- 韩承祚,卫强,徐骁.移植肿瘤学开创肝移植治疗肝癌新时代[J].临床肝胆病杂志,2021,37(2):253-256. DOI:10.3969/j.issn.1001-5256.2021.02.002.
- 林祖源,吴逸超,徐骁.肝细胞癌肝移植受者选择标准的变迁[J/CD].实用器官移植电子杂志,2019,7(1):4-8. DOI:10.3969/j.issn.2095-5332.2019.01.002.
- 汪恺,苏仁义,王周城,等.机械灌注+机械阀下扩大标准供肝的修复与功能提升[J].中华消化外科杂志,2022,21(1):74-78. DOI:10.3760/cma.j.cn115610-20211220-00668.
- 戴清清,赵红川,王国斌,等.边缘供肝及器官功能维护在肝移植中的应用进展[J].器官移植,2020,11(2):304-310. DOI:10.3969/j.issn.1674-7445.2020.02.020.
- Attia M, Silva MA, Mirza DF. The marginal liver donor—an update[J]. Transpl Int, 2008, 21(8): 713-724. DOI:10.1111/j.1432-2277.2008.00696.x.
- 孔维娜,唐纓,张国英.脂肪肝供肝定性定量评估的研究进展[J/CD].实用器官移植电子杂志,2019,7(3):241-244. DOI:10.3969/j.issn.2095-5332.2019.03.021.
- Ferri F, Lai Q, Molinaro A, et al. Donor small-droplet macrovesicular steatosis affects liver transplant outcome in HCV-negative recipients[J]. Can J Gastroenterol Hepatol, 2019, 2019:5862985. DOI:10.1155/2019/5862985.
- Jung YB, Yoo JE, Han DH, et al. Clinical and survival outcomes after hepatectomy in patients with non-alcoholic fatty liver and hepatitis B-related hepatocellular carcinoma[J]. HPB (Oxford), 2021, 23(7): 1113-1122. DOI:10.1016/j.hpb.2020.10.027.
- 中华医学会器官移植学分会.中国肝移植供肝获取技术规范(2019版)[J].临床肝胆病杂志,2019,35(12):2700-2702. DOI:10.3969/j.issn.1001-5256.2019.12.011.
- Wang FS, Fan JG, Zhang Z, et al. The global burden of liver disease: the major impact of China[J]. Hepatology, 2014, 60(6): 2099-2108. DOI:10.1002/hep.27406.
- Pais R, Barritt AS 4th, Calmus Y, et al. NAFLD and liver transplantation: current burden and expected challenges [J]. J Hepatol, 2016, 65(6): 1245-1257. DOI:10.1016/j.jhep.2016.07.033.
- Rinella ME. Nonalcoholic fatty liver disease: a systematic review[J]. JAMA, 2015, 313(22): 2263-2273. DOI:10.1001/jama.2015.5370.
- Zhang QY, Zhang QF, Zhang DZ. The impact of steatosis on the outcome of liver transplantation: a meta-analysis[J]. Biomed Res Int, 2019, 2019:3962785. DOI:10.1155/2019/3962785.
- Vodkin I, Kuo A. Extended criteria donors in liver transplantation[J]. Clin Liver Dis, 2017, 21(2): 289-301. DOI:10.1016/j.cld.2016.12.004.
- 戴清清,赵红川,王国斌,等.边缘供肝及器官功能维护在肝移植中的应用进展[J].器官移植,2020,11(2):304-310. DOI:10.3969/j.issn.1674-7445.2020.02.020.
- Cesaretti M, Addeo P, Schiavo L, et al. Assessment of liver graft steatosis: where do we stand? [J]. Liver Transpl, 2019, 25(3): 500-509. DOI:10.1002/lt.25379.
- Linares I, Hamar M, Selzner N, et al. Steatosis in liver transplantation: current limitations and future strategies [J]. Transplantation, 2019, 103(1): 78-90. DOI:10.1097/TP.0000000000002466.
- Orci LA, Berney T, Majno PE, et al. Donor characteristics and risk of hepatocellular carcinoma recurrence after liver transplantation[J]. Br J Surg, 2015, 102(10): 1250-1257. DOI:10.1002/bjs.9868.
- 田大治,蒋文涛,陈池义,等.中重度脂肪变性供肝应用于成人肝移植术的早期预后及其危险因素分析[J].器官移植, 2020, 11(6): 698-703, 736. DOI:10.3969/j.issn.1674-7445.

- 2020.06.008.
- [24] Wong TC, Fung J, Cui T, et al. The risk of going small: lowering GRWR and overcoming small-for-size syndrome in adult living donor liver transplantation[J]. Ann Surg, 2021,274(6):e1260-e1268. DOI:10.1097/SLA.00000000000003824.
- [25] 林栋栋,卢实春,李宁. 小肝移植与小肝综合征[J]. 首都医科大学学报,2011,32(3):356-360. DOI:10.3969/j.issn.1006-7795.2011.03.009.
- [26] Masuda Y, Yoshizawa K, Ohno, Y, et al. Small-for-size syndrome in liver transplantation: definition, pathophysiology and management[J]. Hepatobiliary Pancreat Dis Int, 2020,19(4):334-341. DOI:10.1016/j.hbpd.2020.06.015.
- [27] Shoji K, Miyairi I, Inoue E, et al. Graft-to-recipient weight ratio associated with tacrolimus metabolism following pediatric living donor liver transplantations[J]. J Pediatr Pharmacol Ther,2019,24(2):138-147. DOI:10.5863/1551-6776-24.2.138.
- [28] Nagai S, Yoshida A, Facciuto M, et al. Ischemia time impacts recurrence of hepatocellular carcinoma after liver transplantation[J]. Hepatology, 2015,61(3):895-904. DOI: 10.1002/hep.27358.
- [29] Cheng C, Geng F, Cheng X, et al. Lipid metabolism reprogramming and its potential targets in cancer[J]. Cancer Commun (Lond), 2018, 38(1): 27. DOI: 10.1186/s40880-018-0301-4.
- [30] 白日兰. 肿瘤脂代谢重编程及其对肿瘤和免疫的影响[J]. 中国肿瘤生物治疗杂志,2021,28(5):511-517. DOI:10.3872/j.issn.1007-385x.2021.05.013.
- [31] 赵静,支政,宋光耀. 脂肪酸代谢与肿瘤靶向治疗新途径[J]. 肿瘤,2014,34(9):868-874. DOI:10.3781/j.issn.1000-7431.2014.09.015.
- [32] Yang F, Zhang Y, Ren H, et al. Ischemia reperfusion injury promotes recurrence of hepatocellular carcinoma in fatty liver via ALOX12-12HETE-GPR31 signaling axis[J]. J Exp Clin Cancer Res,2019,38(1):489. DOI:10.1186/s13046-019-1480-9.
- [33] 高伟东,杨龙龙,尹清臣. 氧化应激反应在边缘供肝移植缺血-再灌注损伤中的作用研究进展[J]. 器官移植,2022,13(1):126-131. DOI:10.3969/j.issn.1674-7445.2022.01.019.
- [34] Jia JJ, Li JH, Yu H, et al. Machine perfusion for liver transplantation: a concise review of clinical trials[J]. Hepatobiliary Pancreat Dis Int,2018,17(5):387-391. DOI:10.1016/j.hbpd.2018.06.003.
- [35] Kim B, Kahn J, Terrault NA. Liver transplantation as therapy for hepatocellular carcinoma[J]. Liver Int, 2020, 40(Suppl 1):116-121. DOI:10.1111/liv.14346.
- [36] 孙超,罗清波,卢修贤,等. 符合米兰标准和杭州标准的肝癌肝移植受者预后回顾性分析[J/CD]. 中华移植杂志:电子版, 2015,9(2):9-13. DOI: 10.3877/cma.j.issn.1674-3903.2015.02.003.
- [37] Xu X, Chen J, Wei Q, et al. Clinical practice guidelines on liver transplantation for hepatocellular carcinoma in China (2018 edition) [J]. Hepatobiliary Pancreat Dis Int,2019,18(4):307-312. DOI:10.1016/j.hbpd.2019.06.010.
- [38] Balachandran VP, Gonen M, Smith JJ, et al. Nomograms in oncology: more than meets the eye[J]. Lancet Oncol,2015, 16(4):e173-e180. DOI:10.1016/S1470-2045(14)71116-7.
- [39] Agopian VG, Harlander-Locke M, Zarrinpar A, et al. A novel prognostic nomogram accurately predicts hepatocellular carcinoma recurrence after liver transplantation: analysis of 865 consecutive liver transplant recipients. J Am Coll Surg, 2015, 220(4): 416-427. DOI: 10.1016/j.jamcollsurg.2014.12.025.

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