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血小板-白蛋白-胆红素评分对肝细胞癌患者肝切除术后教科书式结局的影响

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摘要: 目的 血小板-白蛋白-胆红素(PALBI)评分对肝细胞癌(HCC)患者肝切除术后获得教科书式结局(TO)的影响尚不清楚。拟探索术前不同PALBI评分分级与HCC患者肝切除术后获得TO的关系。方法 回顾性收集四川大学华西医院和资阳市中心医院2013年1月—2022年1月行肝切除术的HCC患者资料。TO定义为无术后30 d内严重并发症、无90 d内患者死亡、无出院后30 d内再住院、无围手术期输血、R0切除、无住院时间延长。计数资料两组间比较采用 χ^2 检验。单因素和多因素Logistic回归分析HCC患者肝切除术后获得TO的影响因素。采用Kaplan-Meier法绘制HCC患者生存曲线,并通过Log-rank检验进行比较。结果 共3 599例患者纳入研究,其中2 369例(65.8%)患者获得TO。多因素Logistic回归分析结果显示,PALBI评分分级(PALBI 2级:OR=1.562,95%CI:1.308~1.864, $P<0.001$;PALBI 3级:OR=2.216,95%CI:1.463~3.359, $P<0.001$)是影响HCC患者术后获得TO的独立危险因素。随着PALBI分级增加,患者获得TO的比率降低。PALBI 1级、2级和3级患者获得TO的比率分别为70.2%、54.2%和38.4%,差异有统计学意义($\chi^2=106.295$, $P<0.001$)。30 d内严重并发症发生率、术后90 d内患者病死率、出院后30 d内再住院率、围手术期输血率、住院时间延长率均随着PALBI评分分级的增加而增加(P 值均 <0.05)。获得TO患者术后1、3、5年无复发生存率分别为79.5%、60.6%和51.5%,总生存率分别为92.1%、80.0%和71.1%;未获得TO患者术后1、3、5年无复发生存率分别为68.5%、52.7%和46.2%,总生存率分别为83.3%、66.0%和57.1%。获得TO的患者无复发生存率和总生存率均显著好于未获得TO的患者(χ^2 值分别为18.936、79.371, P 值均 <0.001)。结论 术前PALBI评分分级影响HCC患者肝切除术后获得TO,PALBI分级越高的患者术后越不易获得TO。通过术前PALBI评分评估,有利于早期发现术后并发症发生的高危人群,提早干预,加强围手术期管理,从而提高患者围手术期安全性和长期预后。

关键词: 癌, 肝细胞; 血小板-白蛋白-胆红素评分; 教科书式结局**基金项目:** 四川省自然科学基金(2024NSFSC0637)

Influence of platelet-albumin-bilirubin score on textbook outcome of patients with hepatocellular carcinoma after hepatectomy

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Abstract: Objective To investigate the influence of platelet-albumin-bilirubin (PALBI) score on the textbook outcome (TO) of patients with hepatocellular carcinoma (HCC) after hepatectomy, as well as the association of different PALBI scores before surgery with the achievement of TO after hepatectomy in HCC patients. **Methods** A retrospective analysis was performed for the data of HCC patients who underwent hepatectomy in West China Hospital of Sichuan University and Ziyang Central Hospital from

January 2013 to January 2022. TO was defined as no serious complication within 30 days after surgery, no death within 90 days, no rehospitalization within 30 days after discharge, no blood transfusion in the perioperative period, RO resection, and no prolongation of hospital stay. The chi-square test was used for comparison of categorical data between two groups. The univariate and multivariate Logistic regression analyses were used to investigate the influencing factors for the achievement of TO after hepatectomy in HCC patients. The Kaplan-Meier method was used to plot the survival curves of HCC patients, and the Log-rank test was used for comparison. **Results** A total of 3 599 patients were included in this study, among whom 2 369 (65.8%) achieved TO. The multivariate Logistic regression analysis showed that PALBI grade (PALBI grade 2: odds ratio [OR]=1.562, 95% confidence interval [CI]: 1.308—1.864, $P<0.001$; PALBI grade 3: OR=2.216, 95%CI: 1.463—3.359, $P<0.001$) was an independent risk factor for achievement of TO after surgery in HCC patients. The proportion of patients achieving TO decreased with the increase in PALBI grade. Among the patients with PALBI grade 1, 2 or 3, the patients achieving TO accounted for 70.2%, 54.2%, and 38.4%, respectively ($\chi^2=106.295$, $P<0.001$). The incidence rate of serious complications within 30 days, the mortality rate of patients within 90 days after hepatectomy, readmission rate within 30 days after discharge, perioperative blood transfusion rate, and the rate of prolonged hospital stay all increased with the increase in PALBI grade (all $P<0.05$). For the patients achieving TO, the 1-, 3-, and 5-year relapse-free survival rates were 79.5%, 60.6%, and 51.5%, respectively, and the overall survival rates were 92.1%, 80.0%, and 71.1%, respectively; for those who did not achieve TO, the 1-, 3-, and 5-year relapse-free survival rates were 68.5%, 52.7%, and 46.2%, respectively, and the overall survival rates were 83.3%, 66.0%, and 57.1%, respectively. The patients who achieved TO had significantly better relapse-free survival rate and overall survival rate than those who did not achieve TO ($\chi^2=18.936$ and 79.371 , both $P<0.001$). **Conclusion** Preoperative PALBI grade can affect the achievement of TO after hepatectomy in HCC patients, and it is more difficult for patients with a higher PALBI grade to achieve TO. Preoperative PALBI score can be used to early identify the patients with a high risk of postoperative complications, provide early intervention, and enhance perioperative management, thereby improving the perioperative safety and long-term prognosis of HCC patients after hepatectomy.

Key words: Carcinoma, Hepatocellular; Platelet-Albumin-Bilirubin Score; Textbook Outcome

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肝细胞癌(HCC)是肝脏最常见的原发性恶性肿瘤,每年导致全球范围内超过80万患者死亡^[1],给社会经济造成巨大负担。由于我国HBV感染率较高,每年新发及死亡的HCC患者约占全球患者的50%^[2]。目前,手术切除是公认的HCC根治性治疗措施之一。近年来,随着麻醉及手术技术、围手术期管理等不断提高,肝切除术已在许多医院常规开展。但是肝切除术是一项复杂程度较高的手术,术后严重并发症及围手术期死亡较为常见。既往文献报道,肝切除术后围手术期严重并发症发生率为23.3%~32%,围手术期病死率为0.3%~3.3%^[3-7]。因此探索影响患者术后并发症发生及围手术期死亡的危险因素,对外科医师治疗方案的选择、并发症的预防等均有一定的指导作用。

既往针对HCC患者围手术期的结局及手术质量的评价常采用单一指标,如并发症发生率、围手术期病死率等。部分学者认为这些单一指标虽然可以从一定程度上评价患者的结局和手术的质量,但是肝切除术作为一项复杂的手术,单一指标往往难以覆盖患者手术的各

个维度^[8]。2013年Kofschoten等^[9]提出了教科书式结局(textbook outcome, TO)的概念,用于评估结直肠癌患者的手术结局。TO是一项复合型指标,通过“全或无”的方式对患者术后的一些重要结局指标进行全面评估。这些指标包括无术后30 d内死亡、根治性切除、无住院时间延长等^[9]。患者只有满足全部指标,才能被定义为获得了TO^[9]。近年来,TO获得了学界的广泛认可,已被用于胰腺手术、食管癌根治术、肝移植等手术的预后和手术质量等评价^[8,10-12]。

HCC患者往往合并肝硬化和门静脉高压。既往研究仅关注肝功能对HCC患者预后的影响,而忽视了门静脉高压在患者预后中的作用。血小板-白蛋白-胆红素(platelet-albumin-bilirubin, PALBI)评分是目前用于评估患者肝功能的指标之一^[13]。该评分同时包括了反映患者肝功能(胆红素、白蛋白)和门静脉高压(血小板)的指标,其是否会影响肝切除患者获得TO目前尚不清楚,故开展本研究予以探索。

1 资料与方法

1.1 研究对象 回顾性收集四川大学华西医院和资阳市中心医院2013年1月—2022年1月行肝切除术的患者资料。纳入标准:(1)患者年龄 ≥ 18 岁;(2)术后病理诊断为HCC。排除标准:(1)患者年龄 < 18 岁;(2)同时合并其他恶性肿瘤;(3)术前肝癌破裂出血者;(4)术前接受抗肿瘤治疗的患者;(5)HCC复发患者;(6)再次接受肝切除术的患者;(7)临床病理资料不完整的患者。

1.2 术后随访 HCC患者术后2年内,每3~4个月随访1次;术后2年以后,每6个月随访复查1次。检查内容包括:肝功能、血常规、肾功能、AFP、异常凝血酶原、HBV DNA、腹部超声或增强CT或磁共振、胸部CT^[14-15]。

1.3 定义 PALBI评分计算公式: $PALBI = 2.02 \times \log_{10}[\text{总胆红素}(\mu\text{mol/L})] - 0.37 \times \{\log_{10}[\text{总胆红素}(\mu\text{mol/L})]\}^2 - 0.04 \times \text{白蛋白}(\text{g/L}) - 3.48 \times \log_{10}[\text{血小板}(10^3/\mu\text{L})] + 1.01 \times \{\log_{10}[\text{血小板}(10^3/\mu\text{L})]\}^2$ ^[13]。PALBI分为3级, ≤ -2.53 分为1级, > -2.53 分且 ≤ -2.09 分为2级, > -2.09 分为3级^[13]。白蛋白-胆红素(albumin-bilirubin, ALBI)评分计算公式: $ALBI = \log_{10}[\text{总胆红素}(\mu\text{mol/L})] \times 0.66 + \text{白蛋白}(\text{g/L}) \times (-0.085)$ ^[16]。ALBI按照如下标准分为3级:1级, ≤ -2.60 分;2级, > -2.60 分但 ≤ -1.39 分;3级, > -1.39 分^[16]。TO的定义为无术后30 d内严重并发症、无90 d内患者死亡、无出院后30 d内再住院、无围手术期输血、R0切除、无住院时间延长^[8, 17-18]。严重术后并发症定义为 \geq Clavien-Dindo分级3级并发症^[8]。住院时间延长定义为术后住院时间 ≥ 8 d(住院时间的第75百分位数)^[8]。预后营养指数(prognostic nutritional index, PNI)计算公式: $PNI = \text{白蛋白}(\text{g/L}) + 5 \times \text{淋巴细胞计数}(10^9/\text{L})$ ^[19]。PNI < 45 视为低营养状态^[19]。

1.4 统计学方法 应用SPSS 29.0统计软件进行数据分析。计量资料以 $\bar{x} \pm s$ 表示。计数资料两组间比较采用 χ^2 检验。单因素和多因素Logistic回归分析HCC患者肝切除术后获得TO的影响因素。采用Kaplan-Meier法绘制HCC患者生存曲线,并通过Log-rank检验进行比较。 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 基线临床病理特征 根据纳入和排除标准,本研究共纳入3 599例HCC患者,其中男3 068例,女531例,平均年龄(52.7 \pm 11.7)岁。AFP > 400 ng/mL的患者有1 313例(36.5%)。ALBI评分结果显示,2 583例(71.8%)患者为ALBI 1级,1 016例(28.2%)患者为ALBI 2级。PALBI评分结果显示,本研究中PALBI 1级、2级、3级的患者分别有2 730例(75.9%)、757例(21.0%)和112例(3.1%)。共369例(10.3%)患者为肝内多发肿瘤,平均肿瘤直径为(5.8 \pm 3.6)cm。术后病理证实1 307例(36.3%)患者存在微血管侵犯(microvascular invasion, MVI)。术前共有580例(16.1%)患者PNI < 45 。185例(5.1%)患者术前血小板计数 $< 50 \times 10^9/\text{L}$ 。根据巴塞罗那临床肝癌分期(Barcelona clinical liver cancer, BCLC),267例(7.4%)患者为BCLC 0期,2 710例(75.3%)患者为BCLC A期,278例(7.7%)患者为BCLC B期,344例(9.6%)患者为BCLC C期。

比较PALBI 1级、2级、3级患者的基线临床病理特征,发现分级更高的患者其AFP > 400 ng/mL、PNI < 45 、HBV DNA阳性、肿瘤直径 > 5 cm、肿瘤低分化、MVI阳性、ALBI 2级和BCLC B/C期占比更高(P 值均 < 0.001) (表1)。

2.2 HCC患者术后TO情况 本研究中共2 369例(65.8%)患者获得TO,余下1 230例(34.2%)患者至少存在一项不满足TO标准的因素,具体如下:57例(1.6%)患者术后90 d

表1 不同PALBI评分分级患者基线临床病理特征比较

Table 1 Comparison of the baseline clinicopathological characteristics of patients with different PALBI grades

项目	PALBI 1级(n=2 730)	PALBI 2级(n=757)	PALBI 3级(n=112)	χ^2 值	P值
男[例(%)]	2 314(84.8)	656(86.7)	98(87.5)	2.161	0.339
年龄 > 65 岁[例(%)]	474(17.4)	130(17.2)	17(15.2)	0.364	0.834
AFP > 400 ng/mL[例(%)]	939(34.4)	315(41.6)	59(52.7)	26.403	< 0.001
PNI < 45 [例(%)]	247(9.0)	258(34.1)	75(67.0)	495.853	< 0.001
HBV DNA阳性[例(%)]	1 025(37.5)	343(45.3)	67(59.8)	34.093	< 0.001
肿瘤直径 > 5 cm[例(%)]	1 164(42.6)	451(59.6)	84(75.0)	104.069	< 0.001
肝内多发肿瘤[例(%)]	276(10.1)	74(9.8)	19(17.0)	5.731	0.057
ALBI 2级[例(%)]	420(15.4)	489(64.6)	107(95.5)	966.901	< 0.001
MVI阳性[例(%)]	936(34.3)	309(40.8)	62(55.4)	29.061	< 0.001
肿瘤低分化[例(%)]	276(10.1)	113(14.9)	20(17.9)	18.493	< 0.001
BCLC B/C期[例(%)]	433(15.9)	157(20.7)	32(28.6)	20.173	< 0.001

内死亡;142例(3.9%)患者为非R0切除;267例(7.4%)患者存在围手术期输血;195例(5.4%)患者术后30d内出现严重并发症;25例(0.7%)患者出院后30d内重返住院;918例(25.5%)患者住院时间延长。随着PALBI评分分级增加,患者获得TO的概率降低。PALBI 1级、2级和3级患者中分别有1916例(70.2%)、410例(54.2%)、43例(38.4%)患者获得TO,差异有统计学意义($\chi^2=106.295, P<0.001$)。

2.3 影响HCC患者术后TO的危险因素分析 单因素 Logistic 回归分析显示,AFP>400 ng/mL、血小板计数< $50\times 10^9/L$ 、PNI<45、ALBI 2级、肿瘤直径>5 cm、肿瘤低分化、MVI阳性、BCLC B/C期、PALBI 2/3级是影响HCC患者术后获得TO的潜在危险因素(P 值均<0.05);进一步多因素 Logistic 回归分析结果表明,血小板计数< $50\times 10^9/L$ 、PNI<45、肿瘤直径>5 cm、MVI阳性、BCLC B/C期、PALBI 分级是影响HCC患者术后获得TO的独立危险因素(P 值均<0.05)(表2)。

2.4 不同PALBI分级患者非TO指标发生率的比较 比

较不同PALBI分级患者非TO指标的发生情况,结果显示,6项指标中除非R0切除外,其余5项指标均随着PALBI分级增加,发生率亦增加(P 值均<0.05)(表3)。

2.5 TO与非TO患者术后无复发生存率(recurrence-free survival, RFS)和总生存率(overall survival, OS)比较 术后获得TO与未获得TO(non-TO)患者RFS及OS结果显示,TO患者术后1、3、5年RFS分别为79.5%、60.6%和51.5%,non-TO患者术后1、3、5年RFS分别为68.5%、52.7%和46.2%,差异有统计学意义($\chi^2=18.936, P<0.001$)(图1a);TO患者术后1、3、5年OS分别为92.1%、80.0%和71.1%,显著好于non-TO患者(1、3、5年OS分别为83.3%、66.0%和57.1%, $\chi^2=79.371, P<0.001$)(图1b)。

3 讨论

既往对肝切除术的结局评价往往采用单一指标,如并发症发生率、围手术期病死率等。这有利于针对某一特定并发症采取有针对性的预防或干预措施,但难以覆盖手术操作及围手术期管理的各个维度,且部分指标受

表2 肝切除术后影响HCC患者获得TO的危险因素分析

Table 2 Risk factors affecting TO achievement in HCC patients after hepatectomy

项目	单因素分析			多因素分析		
	OR	95%CI	P值	OR	95%CI	P值
男性	1.110	0.912 ~ 1.351	0.299			
年龄>65岁	0.972	0.810 ~ 1.167	0.764			
AFP>400 ng/mL	1.403	1.218 ~ 1.617	<0.001			
HBV DNA 阳性	1.089	0.946 ~ 1.253	0.234			
血小板计数< $50\times 10^9/L$	1.365	1.010 ~ 1.864	0.043	1.507	1.096 ~ 2.072	0.012
PNI<45	2.346	1.960 ~ 2.810	<0.001	1.696	1.387 ~ 2.073	<0.001
ALBI 2级	1.994	1.717 ~ 2.316	<0.001			
肿瘤直径>5 cm	2.290	1.989 ~ 2.636	<0.001	1.889	1.622 ~ 2.200	<0.001
多发肿瘤	1.067	0.852 ~ 1.337	0.571			
MVI 阳性	1.712	1.486 ~ 1.973	<0.001	1.293	1.107 ~ 1.510	0.001
肿瘤低分化	1.244	1.006 ~ 1.538	0.044			
BCLC 分期(B/C vs 0/A)	1.848	1.550 ~ 2.202	<0.001	1.398	1.158 ~ 1.687	<0.001
PALBI 1级	1.000			1.000		
PALBI 2级	1.992	1.689 ~ 2.349	<0.001	1.562	1.308 ~ 1.864	<0.001
PALBI 3级	3.777	2.558 ~ 5.576	<0.001	2.216	1.463 ~ 3.359	<0.001

表3 不同PALBI评分分级患者非TO指标情况的比较

Table 3 Comparison of each type of non-TO among patients with different PALBI grades

项目	PALBI 1级(n=2730)	PALBI 2级(n=757)	PALBI 3级(n=112)	χ^2 值	P值
术后90d内死亡	32(1.2)	21(2.8)	4(3.6)	12.688	0.002
非R0切除	108(4.0)	28(3.7)	6(5.4)	0.711	0.701
围手术期输血	151(5.5)	88(11.6)	28(25.0)	84.065	<0.001
术后30d内严重并发症	123(4.5)	54(7.1)	18(16.1)	33.588	<0.001
出院后30d内再住院	15(0.5)	7(0.9)	3(2.7)	7.806	0.020
住院时间延长	600(22.0)	269(35.5)	49(43.8)	77.574	<0.001

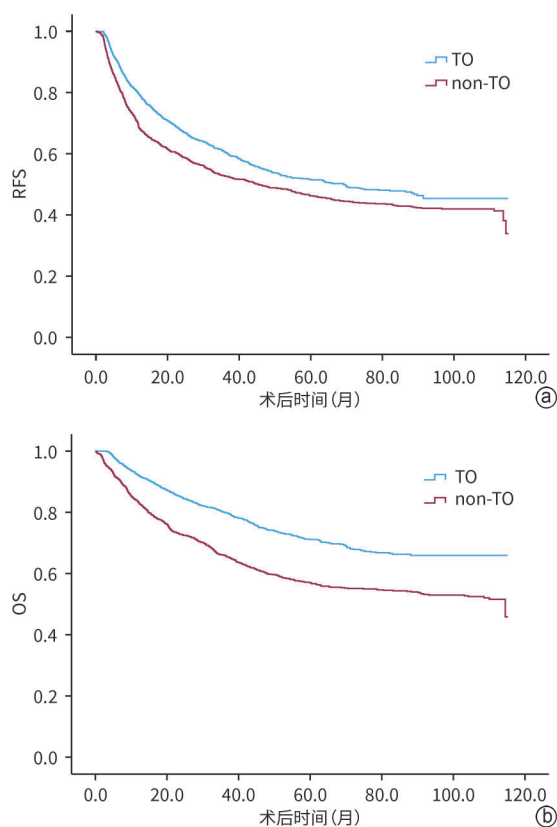


图1 TO与非TO患者RFS及OS的比较
Figure 1 Comparison of recurrence-free survival and overall survival between TO and non-TO patients

发生率和医疗机构实践水平的差异影响较大,从而影响了其临床广泛应用。临床上需要一项综合且稳定的质量评估指标来解决此问题。近年来,TO逐渐被学界认可,用于评价手术质量和患者手术结局情况。TO包含了患者手术和围手术期管理的多项指标,受单一指标的影响相对较小,能更好地反映患者围手术期结局。目前TO已被用于评估多种手术的结局,如胃大部切除术、胰腺十二指肠切除术、食管癌根治术等^[10-12]。并且有学者认为,TO可用于比较不同医疗机构之间同一手术操作的质量^[8,20]。不同手术操作的TO标准并不完全相同,会根据自身特定情况纳入特异性的指标。如van Roessel等^[12]认为,胰腺手术的TO不应有术后胆漏和胰漏;Bonnet等^[11]结合肝移植手术的特殊情况,认为肝移植术后的TO标准应无重症监护室住院时间的延长。但是许多手术的TO标准与本研究采用的标准一样,包含无严重术后并发症、无围手术期死亡、无住院时间延长、无出院后30 d内重返住院和R0切除^[11,21-22]。本研究中所采用的肝切除术后的TO标准已在多项研究中予以采用,具有一定的代表性,得到了一定范围的认可^[8,23]。

本研究证实,PALBI评分能预测HCC患者肝切除术后TO情况。PALBI分级越高的患者,越不易获得TO。PALBI是用于评估患者肝功能的指标之一。既往有研究证实,肝功能越差的HCC患者术后越不容易获得TO。如Tsilimigras等^[24]研究发现,ALBI 1级肝功能的患者较ALBI 2级肝功能的患者更容易获得TO;Xu等^[25]研究亦证实,ALBI 2/3级是HCC患者肝切除术后不能获得TO的独立危险因素。PALBI评分的计算方式与ALBI评分不同,且纳入了血小板这一项与患者门静脉高压相关的指标。术前低血小板计数的患者术中容易出血,术后易出现肝衰竭、感染、围手术期死亡等严重并发症^[26-28]。但在既往的研究中往往忽视了肝硬化门静脉高压对患者预后的影响。这也是PALBI评分相比ALBI评分具有的优势之一。本研究中,尽管ALBI评分在单因素Logistic回归分析中表现出了潜在的预测价值,但是其并不是影响TO的独立危险因素。

本研究结果显示,获得TO的患者RFS和OS均明显好于未获得TO的患者。既往研究表明,HCC术后存在并发症的患者,肿瘤易于复发,生存时间更短^[29-30]。Miyata等^[31]研究认为,术后存在严重并发症的患者更容易在切除术后2年内复发。此外,围手术期输血也会增加患者术后复发和死亡的风险^[32-33]。这也可能是获得TO的患者长期预后更好的原因之一。

本研究还证实,HCC患者术前PNI<45是影响其获得TO的独立危险因素。PNI可以反映患者的营养状态。研究发现,PNI可以预测HCC患者肝切除、肝移植、射频消融等治疗的预后^[34-36]。术前PNI较低的患者,术后肿瘤容易复发,生存期更短^[34-35]。Nagata等^[37]研究发现,术前PNI较低的患者无论接受大范围肝切除还是小范围肝切除,术后并发症发生率均显著高于术前高PNI的患者。Qi等^[30]研究显示,术前低PNI的患者肝切除后肝脏特异性并发症的发生率更高。PNI的计算方式和纳入指标均异于现有的肝功能模型,本研究结果提示,患者术前的营养状态可能也是影响其术后TO的重要因素之一。

本研究亦存在一定的局限性。首先,这是一个回顾性研究,其结论仍需要更多的前瞻性研究予以验证。其次,因我国的HCC患者80%以上均为HBV相关性HCC^[38],PALBI评分对其他病因的HCC患者的预测作用还需要其他研究予以证实。此外,正如本研究多因素Logistic回归分析所示,除患者的肝功能,其肿瘤情况、营养状态等均可能影响获得TO,故纳入患者更多因素的综合预

测模型构建是今后探索的方向。本研究为今后的工作提供了思路。

综上,本研究证实PALBI评分能够预测HCC患者肝切除术后TO的获得情况。PALBI分级越高的患者越不易获得TO。该研究结果有利于早期发现术后并发症发生的高危人群,提早干预,加强围手术期管理,从而提高患者围手术期安全性和长期预后。

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