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·论 著。

术前前白蛋白含量在评估肝癌患者肝切除术后远期预后中的价值

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[关键词] 肝肿瘤;肝细胞癌;肝切除术;前白蛋白;肿瘤复发;生存时间

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Value of preoperative prealbumin content in assessing long-term prognosis of patients with hepatocellular carcinoma after hepatectomy

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Objective To clarify the factors influencing long-term prognosis of patients with hepatocellular Abstract carcinoma (HCC) after hepatectomy, and to explore the value of preoperative plasma prealbumin (PA) in assessing the long-term prognosis. Methods We retrospectively analyzed the clinical and follow-up data of HCC patients who underwent hepatectomy in Eastern Hepatobiliary Surgery Hospital between Dec. 2011 and Mar. 2012. Univariate and multivariate Cox regression analyses were used to analyze the effects of preoperative factors on the overall survival time and recurrence of patients. According to the content of preoperative plasma PA, the patients were divided into high PA group (preoperative PA content was higher than 152 mg/L) and low PA group (preoperative PA content was lower than 152 mg/L); then the difference of prognosis between the two groups were compared by Kaplan-Meier methods. Results A total of 373 HCC patients undergoing hepatectomy were included in this study. The median survival time was 32.3 months and the median recurrence time was 20.5 months. Univariate and multivariate analysis showed that tumor size (P=0.003), TNM stage (P<0.001), preoperative PA content (P=0.034), and vascular invasion (P=0.027) were the independent risk factors for long-term overall survival time of patients after hepatectomy; while TNM stage (P< 0.000 1), preoperative PA content (P=0.002), and vascular invasion (P=0.048) were the independent risk factors for recurrence of patients after hepatectomy. The median overall survival time and median recurrence time of patients in the high PA group were both significantly longer than those in the low PA group, respectively (median overall survival time: 41.3 months vs 31.7 months, $P \le 0.0001$; median recurrence time: 28.8 months vs 14.4 months, $P \le 0.0001$).

Conclusion Low preoperative PA content is an independent risk factor for long-term overall survival and recurrence of HCC patients after hepatectomy.

[Key words] liver neoplasms; hepatocellular carcinoma; hepatectomy; prealbumin; neoplasm recurrence; overall survival

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原发性肝癌(hepatocellular carcinoma, HCC) 是临床最常见的恶性肿瘤之一,随着乙型病毒性肝 炎和丙型病毒性肝炎的广泛传播、逐渐发展,其发生 率逐年升高[1-2]。目前针对 HCC 的治疗方案主要有 手术治疗、肝移植和经皮肝内治疗,且都具有较好的 疗效,但肝切除术是目前国际公认的最适合的治疗 手段[3]。肝功能是判断肝癌患者能否接受手术的主 要因素,以往研究显示,行肝切除术的肝癌患者一般 肝功能是 Child-Pugh A 级或是较早的 B 级^[4]。但 有些经过评估后适合手术的患者术后依然出现了严 重的并发症甚至死亡,有些患者肿瘤复发时间及生 存期较短[5-6]。前白蛋白(prealbumin,PA)是一种由 肝细胞合成的血浆蛋白,只受肝细胞代谢影响,不因 外源性补充而波动,在评估肝功能方面相对于其他 指标如凝血酶原时间(prothrombin time, PT)、白蛋 白(albumin, ALB)更为可靠,既往有研究认为 PA 含量是反映肝脏功能最适合的指标[7]。本研究拟探 讨影响 HCC 患者肝切除术后远期预后的相关术前 肝脏指标,并探讨术前血浆 PA 含量在评价患者远 期预后中的价值。

1 资料和方法

1.1 病例选择 本研究为回顾性研究。收集第二 军医大学东方肝胆外科医院 2011 年 12 月—2012 年 3 月 560 例接受肝切除术的 HCC 患者的病例资 料及随访资料,严格安照制定的纳入标准和排除标 准进行筛选。纳入标准:(1)接受肝切除术的肝癌患 者;(2)切除标本经病理证实为 HCC;(3)预后随访 资料及病例资料完整者。排除标准:(1)合并其他原 发性肿瘤的患者;(2)病例或随访信息不完整者; (3)死亡原因与原发肿瘤无关者;(4)合并影响 ALB 及 PA 含量的其他疾病者。共 373 例纳入本研究, 其中男性 328 例、女性 45 例,中位年龄 52(25~81) 岁。临床病理和术前实验室资料见表 1。

1.2 资料收集 从患者病例资料中收集患者的性别、年龄、乙肝病毒(hepatitis B virus, HBV)感染

史、吸烟史和饮酒史、Child-Pugh 分级、术前实验室 检测指标(PA、ALB、TB、PT、AFP、CA19-9、CEA 值)及病理资料(肿瘤数目、大小、病理形态、血管侵 犯、有无肝硬化)。患者术前资料为患者第1次在我 院住院尚未接受任何治疗之前获得。肿瘤的 TNM 分期结合患者术后病理资料,参照 AJCC 第7版 TNM 分期系统[^{8]}得出。

表 1 患者基本临床病理特征 Tab 1 Basic characteristics of all patients

N = 373Characteristics Data 52(25-81) Age(year), median(range) Gender n(%)Male 328(87.9) Female 45(12, 1) Tumor size d/cm, median(range) 6.0(0.8-20.8) Tumor number n(%)Single 296(79.4) Multiple 77(20.6) PA $\rho_B/(\text{mg} \cdot L^{-1})$, median(range) 194(70-405) PT t/s, median(range) 12.0(10.1-15.5) ALB $\rho_{\rm B}/({\rm g} \cdot {\rm L}^{-1})$, median(range) 40.4(23.8-67.7) AFP $\rho_B/(\mu g \cdot L^{-1})$, median(range) 151. 2(0-1 213 000) TNM stage n(%)Ι 248(66.5) \coprod 59(15.8) 53(14.2) \blacksquare 13(3.5) Tumor differentiation n(%)Well 44(11.8) 309(82.8) Moderate Poor 20(5.4) Vascular invasion n(%)No 338(90.6) 35(9.4) Microscopic tumor thrombus n(%)No 339(90.9) Yes 34(9.1)

PA: Prealbumin; PT: Prothrombin time; ALB: Albumin; AFP: α -Fetoprotein

1.3 临床指标临界值的界定 我院临床使用数据

中,判断 PA 含量高低的临界值为 172 mg/L。为了验证临界值对数据准确性的影响程度,更好地明确 PA 含量对预后的影响,利用 X-tile 软件计算得出 PA 的最佳临界值,使相应组别患者生存期与复发状况比较时的 P 值最小。经过 X-tile 计算,PA 含量以 152 mg/L 为临界值的 P 值为 0.001 9,PA 含量以 172 mg/L 为临界值的 P 值为 0.089 8。说明 PA 含量 152 mg/L 为临界值比 172 mg/L 更有统计学意义。其他临床指标皆以临床临界值作为分组界值。

1.4 病例随访 研究起始时间为接受肝切除术的 术后第1天,结束时间为患者死亡、最后1次随访时 间或失访时间。随访时间截至2016年12月1日, 第1年患者每1个月进行1次随访,第2年每3个 月接受1次随访,第3年及以后每6个月接受1次 随访。随访内容包括患者术后有无复发、复发时间、 生存状态、死亡时间、肝功能、肿瘤血清学指标 (AFP、CEA、CA19-9)及影像学情况(B超、CT、 MRI)。若患者术后肿瘤指标明显增高且大于正常 值,或影像学检测到新的病灶,则定义为肿瘤复发。 随访期间若患者死于原发灶及相关疾病则患者为完 全数据,若截至随访日期患者仍生存则按照截尾数 据处理。

1.5 统计学处理 所有数据采用 Excel 进行统计整理,以 SPSS 22.0 软件进行统计学分析。用单因素 Cox 回归分析得到与预后相关的因素,并用多因素 Cox 回归法得出独立预后因子。根据 PA 临界值 152 mg/L 将患者分为高 PA 组及低 PA 组,采用 χ^2 检验比较两组之间分类资料的差异。以 Kaplan-Meier 曲线评估患者复发率及生存率,并用 Log-rank方法检验两组间的差异。检验水准(α) 为 0.05。

2 结 果

2.1 患者预后危险因素分析 通过单因素分析发现,术前血清 PA 含量、肿瘤数量、肿瘤大小、TNM 分期、肿瘤分化程度、微血管癌栓都是影响 HCC 患者术后生存的危险因素,肿瘤大小、肿瘤数量、术前血清 PA 含量、TNM 分期、血管癌栓是影响 HCC 患者术后肿瘤复发的危险因素;进一步行多因素分析发现,肿瘤大小、TNM 分期、PA 含量、血管癌栓是影响 HCC 患者术后生存的独立危险因素,TNM 分期、PA 含量、血管侵犯是影响 HCC 患者术后肿瘤复发的独立危险因素(表 2)。

表 2 患者生存状态和复发的单因素及多因素分析

Tab 2 Univariate and multivariate analysis of factors influencing overall survival and recurrence of patients

	Overall survival				Recurrence			
Factor -	Univariate		Multivariate		Univariate		Multivariate	
	HR	P value	HR(95%CI)	P value	HR	P value	HR(95%CI)	P value
Sex: male vs female	0.639	0.122			0.709	0.112		
Age: ≤53 years vs >53 years	1.002	0.990			0.843	0.193		
Tumor size: ≤3 cm vs >3 cm	4. 192	<0.0001	3.021(1.465,6.227)	0.003	1.594	0.016		
Tumor number: single vs multiple	2.669	<0.0001			2.141	<0.0001		
TNM stage: I vs II vs III vs IV	1.834	<0.0001	1.602(1.355,1.895)	<0.001	1.593	<0.0001	1. 489(1. 284, 1. 725)	<0.0001
$PA_{:} \leq 152 \text{ mg/L vs} > 152 \text{ mg/L}$	0.522	<0.0001	0.689(0.487,0.973)	0.034	0.568	<0.0001	0.639(0.482,0.846)	0.002
AFP: \leq 20 μ g/L vs $>$ 20 μ g/L	1.300	0.141			1. 274	0.086		
PT: ≤13 s vs >13 s	1.057	0.786			1. 225	0.197		
TB: $\leq 34 \ \mu \text{mol/L vs} > 34 \ \mu \text{mol/L}$	1.621	0.247			1.065	0.880		
ALB: \leq 35 g/L vs $>$ 35 g/L	0.672	0.133			0.788	0.294		
Tumor differentiation: well vs moderate vs poor	1.640	0.008			1.155	0.318		
Vascular invasion: yes vs no	3.103	<0.0001	1.711(1.064,2.753)	0.027	2.392	<0.0001	1.54(1.004,2.360)	0.048

PA: Prealbumin; AFP: α-Fetoprotein; PT: Prothrombin time; TB: Total bilirubin; ALB: Albumin; HR: Hazard ratio; CI: Confidence interval

2.2 PA与患者临床各数据之间的关系 根据 PA 临界值 152 mg/L 将患者分为高 PA 组及低 PA 组,比较 2 组临床病理特征的差异,结果如表 3 所示。由表 3 可见,低 PA 组中肿瘤直径>3 cm、PT> 13 s、TB>34 μmol/L、ALB≤35 g/L 的患者比例高

于高 PA 组 (P<0.05),且低 PA 组中 TNM 分期晚、肿瘤病理分期差、有血管癌栓的患者比例更高 (P<0.05)。患者年龄、性别、肿瘤数量、AFP 含量 在两组间差异无统计学意义。

2.3 PA与患者长期生存的关系 如图 1 所示,低

PA组 HCC 患者的中位生存时间为 31.7 个月,高 PA组 HCC 患者的中位生存时间为 41.3 个月,高 PA组比低 PA组患者获得了更长的总生存时间 (P<0.000 1);低 PA组 HCC 患者肿瘤的中位复发时间为 14.4 个月,高 PA组肝癌患者肿瘤的中位复发发时间为 28.8 个月,高 PA组比低 PA组患者复发时间更长(P<0.000 1)。

表 3 低 PA 组(≤152 mg/L)和高 PA 组 (>152 mg/L)患者临床病理特征的比较

Tab 3 Comparison of clinicopatological characteristics of patients between low PA (≤152 mg/L) and high PA (>152 mg/L) groups

			n
Characteristics	Low PA N=96	High PA N=277	P value
Gender			0. 108
Male	80	248	
Female	16	29	//
Age			0.302
€53 years	43	141	T
>53 years	53	136	15
Size			0.012
≪3 cm	7	50	
>3 cm	89	227	
Tumor number		181	0.129
Single	71	225	14
Multiple	25	52	
TNM stage		39/	0.03
I	52	196	TADE
П	20	39	1111
II	19	34	
IV	5	8	
AFP			0.24
€20 µg/L	26	93	
>20 μg/L	70	184	
PT			< 0.001
≪13 s	59	241	
>13 s	37	36	
ТВ			0.004
\leq 34 μ mol/L	90	274	
$>$ 34 μ mol/L	6	3	
ALB			<0.001
≪35 g/L	20	9	
>35 g/L	76	268	
Tumor differentiation			0.02
Well	4	40	
Moderate	85	224	
Poor	7	13	
Vascular invasion			0.043
No	82	256	
Yes	14	21	

PA: Prealbumin; AFP: α -Fetoprotein; PT: Prothrombin time; TB: Total bilirubin; ALB: Albumin

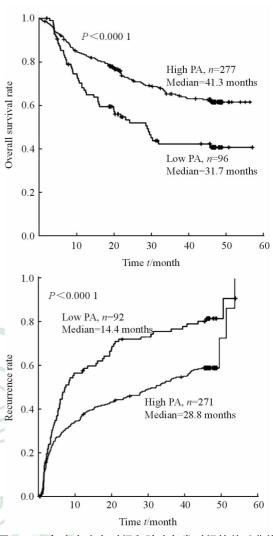


图 1 PA 与患者生存时间和肿瘤复发时间的关系曲线 Fig 1 Correlation of preoperative prealbumin (PA) content with overall survival and recurrence time

3 讨论

HCC是目前发病率及死亡率均居世界前列的恶性肿瘤^[1,5,9]。目前,手术治疗依然是针对肝癌的最佳治疗方式,但患者术后肿瘤复发率高、长期生存情况较差。既往研究表明,肝癌患者的 AFP、肿瘤TNM 分期及肝脏储备功能等因素可以用来预测肝癌患者术后肿瘤的复发风险及生存状态^[10]。但这些指标的水平并不稳定,患者肿瘤堵塞胆管导致 TB升高亦会导致结果波动,AFP水平在术前及术后阴性检测率高达 30%以上^[11-12],而通过 TNM 分期对肝癌预后评估较为准确却存在滞后性,因此探究可靠的术前预测指标具有积极且重要的临床意义^[10]。既往研究表明患者营养状态与术后并发症密切相关,而且也是影响术后肿瘤复发时间及长期生存状态的重要因素^[13]。肿瘤患者的免疫抑制状态为癌

细胞的发生、分裂及扩散提供了良好的微环境[14], 外周血淋巴细胞是机体自身免疫的重要组成部分, 越来越多的研究关注其在肿瘤研究中的潜在价 值[15]。肿瘤患者的另一特征是机体功能的显著下 降及营养状况不良,会导致自身合成 ALB 能力的下 降,故而既往研究中常将 ALB 作为评估患者营养状 态的重要指标[16]。但随着医疗技术的发展,更多的 血浆制品被用于临床,患者通过外周血补充 ALB 的 概率增加[17],加之 ALB 半衰期较长,约 15~19 d, 血浆浓度波动使得术前评估不准确;而且通过静脉 补充 ALB 无法改善肿瘤患者的远期预后[18]。血浆 PA 是一种完全由肝细胞产生的载体蛋白,其主要生 理功能是运输甲状腺素和维生素 A,通过促进淋巴 细胞成熟增强机体的免疫力[19]。研究表明,PA 对 肝细胞损伤具有极强的敏感性和特异性[20-21],因此, PA 比 ALB 更适合作为评价肝癌患者营养状态、监 测营养支持效果的指标。而且,在胃癌[22]、结肠 癌[23]、肺癌[24]中的研究也表明 PA 与患者远期预后 密切相关。

本研究通过预后危险因素分析,发现 PA 是影响肝癌肝切除术患者整体预后的独立危险因素之一。血清 PA 含量较低的 HCC 患者,其肿瘤复发时间较短,总生存期相对缩短。尽管 PA 影响肿瘤患者长期预后的具体机制尚未完全阐明,但免疫抑制在肿瘤的发生发展及复发中的作用已被广泛接受^[25]。PA 促进淋巴细胞的生成,其血清含量越低,淋巴细胞越少,进而造成机体低免疫状态^[15]。由于PA 完全由肝细胞产生,不受静脉补充干扰,具备评估肝细胞状态的能力,可以作为预测患者预后的潜在指标之一。

综上所述,根据本中心研究数据分析,我们认为 PA与肝癌肝切除术患者的肿瘤复发及远期生存状态密切相关,可以作为辅助评估患者预后、选择治疗方案的潜在指标。由于本研究数据基于单中心,纳入病例数较少,其代表性存在一定的局限,这些因素可能会影响本研究结果的普遍性,因此还有待进一步的多中心大样本研究来验证。

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