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· 论 著 ·

乙型肝炎病毒感染对肝内胆管细胞癌预后的影响

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[摘要] **目的** 探讨HBV感染对肝内胆管细胞癌(ICC)预后的影响。**方法** 回顾性分析2015年10月至2019年12月于我院安亭院区入院治疗的162例经手术或穿刺活检病理明确诊断为ICC的患者资料。比较乙型肝炎相关ICC组(55例)和非乙型肝炎相关ICC组(107例)患者的一般资料及预后情况,并采用Cox比例风险回归模型分析影响ICC患者预后的独立因素。**结果** 乙型肝炎相关ICC组及非乙型肝炎相关ICC组患者的中位生存期分别为26、28个月,1、3、5年总生存率分别为80.0%、29.8%、14.5%和79.3%、31.2%、16.6%,1、3、5年无进展生存率分别为59.0%、21.5%、14.3%和52.6%、20.9%、13.1%,两组患者总生存率和无进展生存率差异均无统计学意义($P=0.487$ 、 0.634)。HBV-DNA水平分层分析显示,HBV-DNA ≤ 50 IU/mL组和HBV-DNA > 50 IU/mL组乙型肝炎相关ICC患者的总生存率、无进展生存率差异均无统计学意义($P=0.643$ 、 0.535)。多因素Cox比例风险回归分析显示,TNM分期Ⅳ期($HR=3.12$, 95% CI 1.57~6.20, $P=0.001$)、行根治性手术($HR=0.47$, 95% CI 0.26~0.87, $P=0.016$)、淋巴结转移($HR=2.10$, 95% CI 1.31~3.36, $P=0.002$)是ICC患者总生存的独立影响因素。**结论** 合并HBV感染对ICC患者预后无显著性影响。行根治性手术是ICC患者总生存的独立保护因素,TNM分期Ⅳ期和淋巴结转移是独立危险因素。

[关键词] 乙型肝炎病毒;感染;肝内胆管细胞癌;预后;存活率分析;危险因素

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Prognostic impact of hepatitis B virus infection on intrahepatic cholangiocarcinoma

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[Abstract] **Objective** To investigate the impact of hepatitis B virus (HBV) infection on the prognosis of intrahepatic cholangiocarcinoma (ICC). **Methods** The data of 162 patients with ICC histologically proven by surgery or biopsy in Anting branch of our hospital from Oct. 2015 to Dec. 2019 were retrospectively analyzed. The general information and prognosis of patients with HBV-related ICC (55 cases) and non-HBV-related ICC (107 cases) were compared. Cox proportional hazard regression model was used to analyze the independent factors affecting the prognosis of ICC patients. **Results** The median survival time of patients in HBV-related ICC group and non-HBV-related ICC group were 26 and 28 months, and the 1-, 3- and 5-year overall survival rates were 80.0%, 29.8%, 14.5% and 79.3%, 31.2%, 16.6%, and the 1-, 3- and 5-year progression-free survival rates were 59.0%, 21.5%, 14.3% and 52.6%, 20.9%, 13.1%, respectively. There were no significant differences in overall survival rate or progression-free survival rate between the 2 groups ($P=0.487$, 0.634). Stratified analysis by HBV-DNA levels showed no significant difference in overall survival rate or progression-free survival rate between patients with HBV-related ICC in the HBV-DNA ≤ 50 IU/mL group and HBV-DNA > 50 IU/mL group ($P=0.643$, 0.535). Multivariate Cox proportional hazards regression analysis showed that TNM stage IV (hazard ratio [HR]=3.12, 95% confidence interval [CI] 1.57-6.20, $P=0.001$), radical surgery ($HR=0.47$, 95% CI 0.26-0.87, $P=0.016$) and lymph node metastasis ($HR=2.10$, 95% CI 1.31-3.36, $P=0.002$) were the independent influencing factors of overall survival in ICC patients. **Conclusion** HBV infection has no significant effect on the prognosis of ICC patients. Radical surgery is an independent protective factor for overall survival of ICC patients, and TNM stage IV and lymph node metastasis are the independent risk factors.

[Key words] hepatitis B virus; infection; intrahepatic cholangiocarcinoma; prognosis; survival analysis; risk factors

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肝内胆管细胞癌(intrahepatic cholangiocarcinoma, ICC)是发病率仅次于肝细胞肝癌的原发性肝癌,其恶性程度高、预后较肝细胞肝癌差^[1],其病死率在全球范围内呈逐年上升趋势^[2]。ICC的发病因素很多,胆道囊肿、胆管炎、胆道结石、肝硬化、乙型肝炎、丙型肝炎是ICC发生的主要危险因素^[3]。乙醇摄入、非酒精性脂肪性肝病、糖尿病、肥胖也是ICC的危险因素^[4-7]。不同病因对ICC预后影响不同,其中HBV感染对ICC预后的影响目前结论不一。有研究将乙型肝炎相关ICC与其他危险因素引起的ICC进行比较发现,乙型肝炎相关ICC患者预后较好^[8]。另有研究显示,伴有HBV感染的ICC患者和没有任何主要危险因素的ICC患者相比,两者的生存率和复发率差异均无统计学意义^[9-11]。也有研究认为,与无HBV感染的ICC患者相比,有HBV感染的ICC患者表现出不同的临床病理特征和较低的生存率^[12]。本研究通过回顾性分析162例ICC患者资料,探讨HBV感染对ICC预后的影响。

1 资料和方法

1.1 研究对象 收集2015年10月至2019年12月于海军军医大学(第二军医大学)东方肝胆外科医院安亭院区入治疗的180例经手术或穿刺活检病理明确诊断为ICC的患者资料。排除标准:

(1)合并严重心、脑、肺、肾等疾病;(2)合并其他类型的恶性肿瘤。剔除结石相关ICC患者。最终本研究共有162例(含6例外院确诊病例,最早确诊日期为2014年11月)ICC患者入组,其中乙型肝炎相关ICC患者55例,丙型肝炎相关ICC患者1例,血吸虫相关ICC患者4例,无明确病因ICC患者102例。

1.2 研究分组与观察指标 根据是否合并HBV感染,即乙型肝炎表面抗原(hepatitis B surface antigen, HBsAg)是否阳性,将162例患者分为乙型肝炎相关ICC组(55例)和非乙型肝炎相关ICC组(107例)。所有入组病例中无隐匿性HBV感染患者。收集所有入组患者确诊ICC时的基线资料,包括性别、年龄、病因(乙型肝炎或其他)、治疗方式[手术、化学治疗、局部治疗(放射治疗或肝动脉化疗栓塞术)或系统治疗(免疫治疗或靶向治疗)]、病理分型(低、中、高分化)、TNM分期(I、II、III、IV期)、有无淋巴结转移、有无血管侵犯、是否合并肝硬化,以及血清总胆红素、 γ -谷氨酰转氨酶、甲胎蛋白、CA 19-9和癌胚抗原水平。其中,TNM分期参照第8版AJCC ICC分期标准^[13]。

通过门诊、住院及电话随访患者生存状况,分析两组患者的总生存期及无进展生存期。总生存期定义为自确诊ICC开始至死亡或随访截止日期的时间。无进展生存期定义为自确诊ICC开始至肿瘤进展或随访截止日期的时间。随访截止时间为2020年10月30日或患者死亡。采用实体瘤疗效评价标准(response evaluation criteria in solid tumors, RECIST)评价疗效。

1.3 统计学处理 应用SPSS 25.0软件进行统计学分析。计数资料以例数和百分数表示,两组间比较采用 χ^2 检验或Fisher确切概率法;采用Kolmogorov-Smirnov方法进行正态性检验,符合正态分布的计量资料以 $\bar{x} \pm s$ 表示,两组间比较采用独立样本 t 检验;不符合正态分布的计量资料以中位数(下四分位数,上四分位数)表示,两组间比较采用Mann-Whitney U 检验。采用Kaplan-Meier法计算总生存率及无进展生存率并描绘生存曲线,组间比较采用log-rank检验。采用Cox比例风险回归模型分析影响ICC患者预后的独立因素。检验水准(α)为0.05。

2 结果

2.1 两组患者基线资料比较 162例ICC患者中乙型肝炎相关ICC组55例,男41例、女14例,年龄为(52.69 ± 9.32)岁;非乙型肝炎相关ICC组107例,男60例、女47例,年龄为(61.25 ± 10.88)岁。两组患者的病理类型、TNM分期、治疗方式、淋巴结转移、血管侵犯及血生物化学指标的差异均无统计学意义(P 均 >0.05);但乙型肝炎相关ICC组男性发病率较高、年龄较小、合并肝硬化的患者比例较高,与非乙型肝炎相关ICC组相比差异均有统计学意义(P 均 <0.05)。见表1。

2.2 两组患者Kaplan-Meier生存分析 见图1A,乙型肝炎相关ICC组患者的中位总生存期为26(2~70)个月,1、3和5年总生存率分别为80.0%、29.8%和14.5%;非乙型肝炎相关ICC组患者的中位生存期为28(0~71)个月,1、3和5年总生存率分别为79.3%、31.2%和16.6%。两组患者的总生存率差异无统计学意义($P=0.487$)。见图1B,乙型肝炎相关ICC组患者的中位无进展生存期为16(0~70)个月,1、3和5年无进展生存率分别为59.0%、21.5%和14.3%;非乙型肝炎相关ICC组患者的中位无进展生存期为15(0~65)个月,1、3和5年无进展生存率分别为52.6%、20.9%和13.1%。两组患者的无进展生存率差异无统计学意义($P=0.634$)。

表1 两组 ICC 患者基线资料比较

Tab 1 Baseline data of 2 groups of ICC patients

Index	HBV-related ICC <i>N</i> =55	Non-HBV-related ICC <i>N</i> =107	Statistic	<i>P</i> value
Gender, <i>n</i> (%)			Fisher exact test	0.026
Male	41 (74.5)	60 (56.1)		
Female	14 (25.5)	47 (43.9)		
Age/year, $\bar{x} \pm s$	52.69 $\pm$ 9.32	61.25 $\pm$ 10.88	<i>t</i> =4.967	<0.01
Pathological type, <i>n</i> (%)			$\chi^2=0.520$	0.771
Low differentiation	9 (16.3)	17 (15.9)		
Medium differentiation	46 (83.6)	89 (83.2)		
High differentiation	0	1 (0.9)		
TNM stage, <i>n</i> (%)			$\chi^2=2.802$	0.423
I	19 (34.5)	26 (24.3)		
II	19 (34.5)	39 (36.4)		
III	8 (14.5)	29 (23.4)		
IV	9 (16.4)	13 (15.9)		
Radical surgery, <i>n</i> (%)	14 (25.5)	23 (21.5)	Fisher exact test	0.561
Chemotherapy, <i>n</i> (%)	19 (34.5)	34 (31.8)	Fisher exact test	0.727
Local treatment, <i>n</i> (%)	20 (36.3)	29 (27.1)	Fisher exact test	0.279
Systematic treatment, <i>n</i> (%)	5 (9.0)	9 (8.4)	Fisher exact test	1.000
Lymph node metastasis, <i>n</i> (%)	19 (34.5)	43 (40.2)	Fisher exact test	0.501
Vascular invasion, <i>n</i> (%)	9 (16.4)	15 (14.0)	Fisher exact test	0.816
Cirrhosis, <i>n</i> (%)	17 (30.9)	5 (4.7)	Fisher exact test	<0.01
Total bilirubin/($\mu\text{mol} \cdot \text{L}^{-1}$), <i>M</i> (Q_L , Q_U)	14.30 (10.20, 17.70)	12.70 (9.17, 17.15)	<i>U</i> =0.364	0.364
GGT/($\text{U} \cdot \text{L}^{-1}$), <i>M</i> (Q_L , Q_U)	60.00 (26.00, 107.00)	70.00 (33.00, 145.75)	<i>U</i> =0.089	0.089
Albumin/($\text{g} \cdot \text{L}^{-1}$), $\bar{x} \pm s$	41.86 $\pm$ 4.71	41.72 $\pm$ 4.47	<i>t</i> =0.176	0.860
CA 19-9/($\text{U} \cdot \text{mL}^{-1}$), <i>M</i> (Q_L , Q_U)	29.80 (13.00, 177.40)	44.70 (14.80, 315.95)	<i>U</i> =0.218	0.218
AFP/($\text{ng} \cdot \text{mL}^{-1}$), <i>M</i> (Q_L , Q_U)	3.60 (2.30, 9.20)	3.40 (2.40, 5.92)	<i>U</i> =0.569	0.569
CEA/($\text{ng} \cdot \text{mL}^{-1}$), <i>M</i> (Q_L , Q_U)	3.00 (1.70, 5.00)	2.90 (1.77, 5.15)	<i>U</i> =0.727	0.727

ICC: Intrahepatic cholangiocarcinoma; HBV: Hepatitis B virus; GGT: γ -glutamyltransferase; CA 19-9: Carbohydrate antigen 19-9; AFP: α -fetoprotein; CEA: Carcinoembryonic antigen; *M* (Q_L , Q_U): Median (lower quartile, upper quartile).

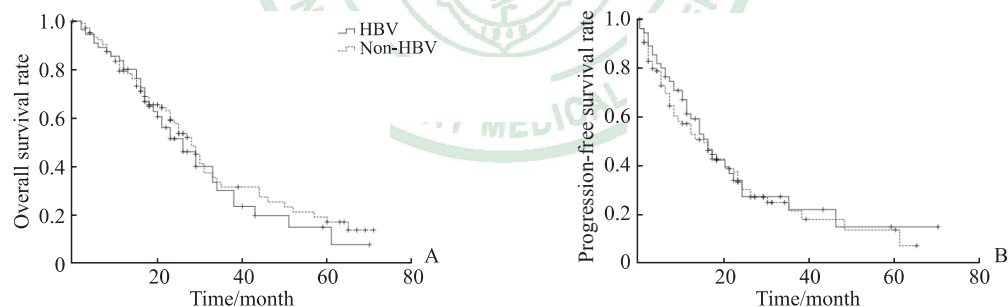


图1 两组 ICC 患者 Kaplan-Meier 生存曲线

Fig 1 Kaplan-Meier survival curves of ICC patients in 2 groups

A: Overall survival; B: Progression-free survival. ICC: Intrahepatic cholangiocarcinoma; HBV: Hepatitis B virus.

2.3 乙型肝炎相关 ICC 患者分层后 Kaplan-Meier 生存分析 根据 HBV-DNA 水平,将乙型肝炎相关 ICC 组患者分为 HBV-DNA ≤ 50 IU/mL 和 HBV-DNA > 50 IU/mL 两组。其中, HBV-DNA ≤ 50 IU/mL 组的 1、3、5 年总生存率分别为 81.0%、34.7%、26.0%, 无进展生存率分别为 57.1%、21.4%、10.7%; HBV-DNA > 50 IU/mL 组的 1、3、5 年总生存率分别为 5.3%、51.3%、7.1%, 无进展生存率分别为 59.9%、16.0%、16.0%。两组患者的总生存率、无进展生存率差异均无统计学意义 ($P=0.643$ 、0.535)。见图 2。

2.4 ICC 患者总生存影响因素的单因素和多因素 Cox 比例风险回归分析 单因素分析结果显示,肿瘤低分化、TNM 分期 IV 期、行根治性手术、行化学治疗、淋巴结转移、血管侵犯、白蛋白 < 35 g/L 是 ICC 患者总生存的影响因素 (P 均 < 0.05)。进一步多因素分析结果显示, TNM 分期 IV 期 ($HR=3.12$, 95% CI 1.57~6.20, $P=0.001$)、行根治性手术 ($HR=0.47$, 95% CI 0.26~0.87, $P=0.016$)、淋巴结转移 ($HR=2.10$, 95% CI 1.31~3.36, $P=0.002$) 是 ICC 患者总生存的独立影响因素。见表 2。

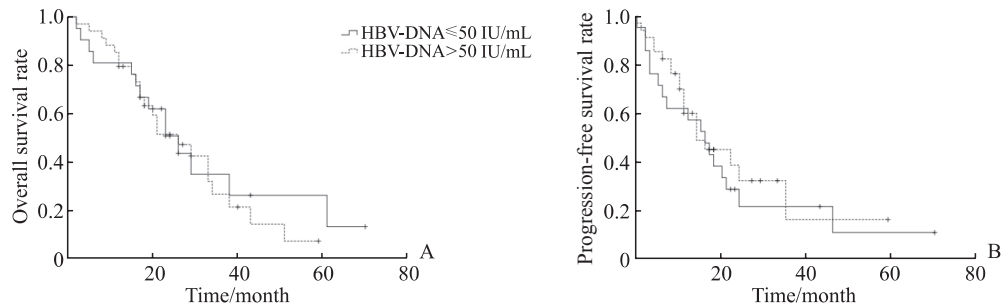


图2 不同 HBV-DNA 水平的乙型肝炎相关 ICC 患者 Kaplan-Meier 生存曲线

Fig 2 Kaplan-Meier survival curves of HBV-related ICC patients with different HBV-DNA levels

A: Overall survival; B: Progression-free survival. HBV: Hepatitis B virus; ICC: Intrahepatic cholangiocarcinoma.

表2 ICC 患者预后影响因素的单因素和多因素 Cox 比例风险回归分析

Tab 2 Univariate and multivariate Cox proportional hazard regression analyses of prognostic influencing factors in

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
HBV infection	1.15 (0.76, 1.73)	0.493		
Male	1.12 (0.74, 1.68)	0.581		
Age>65 years	1.09 (0.71, 1.67)	0.680		
Lowly differentiated tumor	2.21 (1.32, 3.71)	0.002	1.51 (0.86, 2.67)	0.149
TNM stage IV	5.80 (3.39, 9.92)	<0.01	3.12 (1.57, 6.20)	0.001
Radical surgery	0.20 (0.13, 0.31)	<0.01	0.47 (0.26, 0.87)	0.016
Chemotherapy	1.52 (1.01, 2.29)	0.041	1.31 (0.84, 2.04)	0.221
Local treatment	1.12 (0.74, 1.70)	0.570		
Systematic treatment	1.73 (0.94, 3.18)	0.074		
Lymph node metastasis	2.96 (1.98, 4.44)	<0.01	2.10 (1.31, 3.36)	0.002
Vascular invasion	2.06 (1.25, 3.42)	0.005	1.82 (0.98, 3.39)	0.057
Cirrhosis	1.57 (0.94, 2.62)	0.083		
Total bilirubin>35 $\mu\text{mol}\cdot\text{L}^{-1}$	0.73 (0.29, 1.80)	0.500		
GGT>60 $\text{U}\cdot\text{L}^{-1}$	1.38 (0.92, 2.06)	0.114		
Albumin<35 $\text{g}\cdot\text{L}^{-1}$	2.06 (1.07, 3.97)	0.030	1.11 (0.49, 2.48)	0.792
CA 19-9>200 $\text{U}\cdot\text{mL}^{-1}$	1.42 (0.92, 2.20)	0.111		
AFP>100 $\text{ng}\cdot\text{mL}^{-1}$	2.00 (0.80, 5.02)	0.136		
CEA>40 $\text{ng}\cdot\text{mL}^{-1}$	1.91 (0.88, 4.16)	0.102		

ICC: Intrahepatic cholangiocarcinoma; HBV: Hepatitis B virus; GGT: γ -glutamyltransferase; CA 19-9: Carbohydrate antigen 19-9; AFP: α -fetoprotein; CEA: Carcinoembryonic antigen; HR: Hazard ratio; CI: Confidence interval.

3 讨论

ICC 是第二常见的原发性肝癌,也是最不常见的胆管癌,起源于肝内胆管上皮细胞。鉴于其逐渐上升的发病率和病死率^[2,14],本研究回顾性研究了特定病因对 ICC 预后的影响。

本研究中,有 HBV 感染的 ICC 患者发病年龄较早,平均年龄为 (52.6±9.32) 岁,和其他研究结果^[10]一致;相比非乙型肝炎相关 ICC 组,乙型肝炎相关 ICC 组男性发病率较高,且合并肝硬化的患者比例也较高。这些临床特征和肝细胞肝癌相似。较无 HBV 感染的肝细胞肝癌患者,合并 HBV 感染的 ICC 患者亦多见于年轻男性,合并肝硬化的患者

比例更高^[15]。这可能和以下原因有关:(1)乙型肝炎相关 ICC 与乙型肝炎相关肝细胞肝癌有相同的病毒感染;(2)两者有共同的肿瘤干细胞起源,都由肝祖细胞引起^[16];(3)两者有相同的致病过程,HBV 感染肝祖细胞间接造成肝内胆管上皮细胞感染 HBV 而导致癌变;HBV 致肝细胞损伤后产生炎症介质,导致末梢胆管上皮细胞所处基质环境发生改变^[17]。

本研究结果显示,HBV 感染对 ICC 患者的预后无显著影响。尽管 HBV 感染参与了 ICC 的致病过程,导致其与乙型肝炎相关肝细胞肝癌有相似的临床特征,但 ICC 与肝细胞肝癌仍为 2 种不同病理类型的肿瘤,因此导致合并 HBV 感染在 ICC 患者

的预后方面并未显示出独立作用。也可能因为本研究样本量不大,尚未能显示出统计学差异。

本研究表明TNM分期Ⅳ期、是否行根治性手术、有无淋巴结转移是ICC患者总生存的独立影响因素,这和其他研究结果^[10,18-20]一致。其中TNM分期Ⅳ期是ICC患者总生存的独立危险因素,这可能是因为本研究入组患者的TNM分期均参照第8版AJCC ICC分期标准,即远处转移是ICC患者预后的危险因素。

综上所述,合并HBV感染不是ICC患者预后的独立影响因素,TNM分期Ⅳ期、行根治性手术、淋巴结转移是ICC总生存的独立影响因素。本研究结果尚待更大样本量的前瞻性研究进一步证实。

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