Comparison of clinicopathological characteristics between cirrhotic and non-cirrhotic patients with intrahepatic cholangiocarcinoma: A large-scale retrospective study

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Abstract. The effect of cirrhosis on the characteristics of intrahepatic cholangiocarcinoma (ICC) has not been fully elucidated. The purpose of this study was to investigate how cirrhosis affects the clinicopathological characteristics and survival of surgically treated ICC patients. A total of 1,312 ICC patients surgically treated between January 2007 and December 2011 at a single institution were retrospectively reviewed and the clinicopathological data were compared between cirrhotic and non-cirrhotic patients. Univariate and multivariate analyses were performed to identify significant and independent prognostic factors in this cohort. A total of 302 patients (23.0%) were cirrhotic. Compared with cirrhotic patients, the tumors in non-cirrhotic patients were usually larger, less differentiated, and more likely to have lymphatic metastasis, vascular and perineural invasion. Following resection, cirrhotic patients achieved a longer survival compared with non-cirrhotic patients (16.0 vs. 13.0 months, respectively; P<0.038). Multivariate analysis demonstrated that hepatitis B virus infection and cirrhosis were independent favorable prognostic factors, while the presence of cholelithiasis, elevated carbohydrate antigen 19-9 and carcinoembryonic antigen levels, multiple tumors, lymphatic metastasis, vascular invasion and positive surgical margin status were independent unfavorable prognostic factors. Overall, the clinicopathological characteristics of ICC patients with and without cirrhosis differed significantly. Compared with cirrhotic patients, in whom the biological behavior of ICC was similar to that of HCC, non-cirrhotic patients exhibited higher-risk pathological characteristics, lower curative resection rate and worse survival.

Introduction

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver cancer after hepatocellular carcinoma (HCC) (1-3). ICC has been categorized as peripheral and perihilar types based on location (1,4), and as mass-forming, periductular infiltrating and intraductal growth types, based on the growth pattern classification of ICC by the Liver Cancer Study Group of Japan (5). An increasing number of studies suggest that surgical resection usually offers the possibility of long-term survival to patients with this disease (2,6,7). Although there has been a worldwide increase in the incidence and mortality of ICC in recent years (2,3), ICC has not been investigated as extensively as HCC (1).

Previous studies suggested that hepatitis B virus (HBV) infection and cirrhosis, which are well-documented pathogenic factors in the development of HCC (8-11), may also be associated with an increased risk of ICC (12-15). Cirrhosis is common among HCC patients (8-10), and has been proven to be a poor prognostic factor following surgical treatment of HCC (10,16,17). A significant proportion of ICC patients are also cirrhotic; however, the prognostic role of this finding has not been extensively investigated. Although HBV infection has been reported to be a favorable prognostic factor for ICC patients and the clinicopathological characteristics differ between patients with and those without HBV infection (13,18,19), the role of cirrhosis in the prognosis of ICC patients has not been fully elucidated due to the limited number of related studies. Cirrhosis has been found to be a favorable prognostic factor for ICC patients in our former study (20); however, the opposite result was reported by another previous study (21). The aim of the present study was to determine the effect of cirrhosis on the prognosis of ICC patients and the

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Abbreviations: AFP, α-fetoprotein; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CT, computed tomography; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; LN, lymph node; MRI, magnetic resonance imaging; MST, median survival time; OS, overall survival

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mechanism underlying this effect through comparing clinicopathological characteristics and survival data in large series of ICC patients with and without cirrhosis.

Patients and methods

Patients recruiting and grouping. A retrospective study was undertaken, including all consecutive patients with ICC who were admitted to the Eastern Hepatobiliary Surgery Hospital (Shanghai, China) for initial surgical treatment between January 2007 and December 2011. The inclusion criteria were as follows: No history of previous anticancer therapy and no history of other malignancies; no severe comorbidities that may affect survival; potentially resectable ICC on preoperative imaging; and no general contraindications to surgery. The exclusion criteria were as follows: Hilar or extrahepatic cholangiocarcinoma; combined HCC and cholangiocarcinoma; periductular infiltrating type and intraductal growth pattern of ICC; Child's C liver function; hepatitis C virus infection; definitive distant metastasis beyond the abdomen; and incomplete survival data. The patients were identified through computerized hospital databases. Subsequently, demographic data were collected for each patient, including age, gender, symptoms, underlying liver diseases, imaging findings, laboratory tests and pathological results. The patients were divided into two groups according to the presence or absence of cirrhosis, which was defined as widespread disruption of normal liver structure by the formation of pseudolobules or Scheuer stage 4 fibrosis in pathological findings (22). The protocol of the present study was approved by the local Ethics Committee.

Preoperative workup. The preoperative workup included abdominal ultrasonography, computed tomography (CT) and/or magnetic resonance imaging (MRI), cardiac and pulmonary function testing, endoscopic examination and laboratory tests. For patients with local or complete biliary obstruction, endoscopic retrograde cholangiopancreatography or magnetic resonance cholangiopancreatography was performed. In patients with suspected metastasis, positron emission tomography (PET) and CT (PET-CT) was performed.

Surgery. Patients underwent R0 (curative) or R1 (microscopic infiltration of the resection margin) liver resection, apart from cases where distant metastases, peritoneal carcinomatosis, extensive vascular involvement and/or multiple intrahepatic metastases were identified intraoperatively. R2 (palliative) resection and exploratory laparotomy with biopsy intention prior to surgery were not recommended, except when the abovementioned unfavorable findings during intraoperative exploration were beyond the preoperative evaluation of ICC and R0/R1 resection could not be performed. The majority of the liver resections were performed under vascular control, and anatomical or non-anatomical hepatectomy was determined depending on the size and location of tumor, as well as on the background of chronic liver disease. The types of hepatic resection performed included segmentectomy or local resection, bisegmentectomy, right or left hemihepatectomy, and extended hemihepatecomy, according to the 2000 Brisbane Classification of the International Hepato-Pancreato-Biliary Association (23). Additional procedures included cholecystectomy, resection of the biliary confluence and extrahepatic bile duct with Roux-en-Y hepatojejunostomy, portal vein cancerous thrombectomy, and vascular reconstruction. In patients with R0/R1 liver resection and suspected lymph node (LN) metastasis, LN dissection was performed when possible. In other patients with R0/R1 tumor resection and without evidence of macroscopic LN enlargement, preventive skeletonization of the hepatoduodenal ligament was performed to confirm the stage.

Pathological and immunohistochemical methods. All the resected and bioptic specimens were pathologically examined, including tumor size and number, capsule formation, LN metastasis, vascular invasion, perineural invasion and tumor cell differentiation. Each tumor was staged according to the 7th edition of the American Joint Committee on Cancer (AJCC) staging system for ICC (24). The surgical margins were examined for the presence of residual tumor and were classified according to the R classification as R0 (no residual tumor and resection margin >0 mm), R1 (microscopic residual tumor or null-margin resection) or R2 (macroscopic residual tumor) (25). Curative resection was defined a negative resection margin on histopathological examination.

Follow-up. All the patients were followed up postoperatively by X-ray of the chest, ultrasound scan of the liver, liver function tests and serum levels of carbohydrate antigen (CA) 19-9, carcinoembryonic antigen (CEA) and α-fetoprotein (AFP) at an interval of 1-3 months. When recurrence or metastasis were suspected, a CT or MRI scan was performed to confirm the diagnosis. Treatments for recurrent disease included surgery, transarterial chemoembolization, radiotherapy and supportive therapy. Survival was evaluated from the date of surgery; the patients were followed up for survival until death or until the study deadline date of September 30, 2014.

Statistical analysis. Continuous variables are presented as the mean ± standard deviation or as median values and range. Categorical variables are presented as total and percentage. Comparisons were performed using the unpaired t-test for continuous variables and the Chi-squared or Wilcoxon test for categorical variables. Overall survival (OS) rates were calculated using the Kaplan-Meier method. The statistically significant prognostic factors were analyzed by univariate analysis, evaluated using the Kaplan-Meier method and compared with the log-rank test. The multivariate analysis was performed using the Cox proportional hazards model to identify the independent prognostic factors for survival. Statistical analysis was performed using the SPSS 19.0 software for Windows (SPSS Inc., Chicago, IL). Differences with P-values of <0.05 were considered statistically significant.

Results

Clinical characteristics. A total of 1,312 patients with ICC were recruited, with a male predominance (896 patients; 68.3%) and a median age of 54 years (range, 18-82 years). The patients included 302 (23.0%) with and 1,010 (77.0%) without cirrhosis. The differences in clinical characteristics between the two groups of patients are listed in Table I. Compared with patients without cirrhosis, those with cirrhosis were younger,

Table I. Comparison of clinical characteristics between intrahepatic cholangiocarcinoma patients with and without cirrhosis.

Characteristics	With cirrhosis, n (%) (n=302)	Without cirrhosis, n (%) (n=1,010)	P-value
Age (years)			<0.001
Mean ± standard deviation	51.65±10.05	54.80±11.07	
Gender			<0.001
Male	270 (89.4)	626 (62.0)	
Female	32 (10.6)	384 (38.0)	
Symptoms			<0.001
No	155 (51.3)	344 (34.1)	
Yes	147 (48.7)	666 (65.9)	
HBsAg positivity	272 (90.1)	326 (32.3)	<0.001
Alcoholic	59 (19.5)	131 (13.0)	0.004
Schistosomiasis	7 (2.3)	64 (6.3)	0.007
Cholelithiasis	30 (9.9)	224 (22.2)	<0.001
Elevated AFP level	119 (39.4)	129 (12.8)	<0.001
Elevated CA19-9 and/or CEA level	143 (47.4)	633 (62.7)	<0.001
Albumin (g/l)			0.164
Mean ± standard deviation	41.53±3.97	41.91±4.29	
Bilirubin (μmol/l)			0.016
≤20	243 (80.5)	870 (86.1)	
>20	59 (19.5)	140 (13.9)	
ALT(U/l)			0.001
≤42	197 (65.2)	759 (75.1)	
>42	105 (34.8)	251 (24.9)	

AFP, α-fetoprotein; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; HBsAg, hepatitis B surface antigen; ALT, alanine aminotransferase.

included a higher percentage of men, and fewer had symptoms, elevated serum levels of CA19-9 and/or CEA or other concurrent liver diseases, such as schistosomiasis and cholelithiasis; however, a higher percentage of cirrhotic patients had elevated serum levels of AFP.

Pathological characteristics. On pathological examination, more patients without cirrhosis had well/moderately differentiated tumors, while more patients with cirrhosis had tumors with capsule formation (Table II). Patients with cirrhosis had relatively smaller tumors, with a lower likelihood of LN metastasis and perineural invasion, but with a higher likelihood of vascular invasion when compared with patients without cirrhosis. According to the 7th edition of the AJCC staging system, 506 cases (38.6%) were stage I, 323 (24.5%) were stage II, 103 (7.9%) were stage III and 380 (29.0%) were stage IV; more patients with cirrhosis had tumors at an earlier stage compared with those without cirrhosis (Table II).

Surgical results. Of the 1,312 ICC patients undergoing surgery, 1,260 received tumor resection (overall resectability rate, 96.0%), among whom 296 (98.0%) were cirrhotic and 964 (95.4%) were non-cirrhotic. The types of liver resection included extended right or left hemihepatectomy in 69 (5.3%), right or left hemihepatectomy in 424 (32.3%), bisegmentectomy in 517 (39.4%), and segmentectomy or local resection in 250 (19.1%) patients; in patients with multiple tumors, different types of liver resections were used in combination, depending on the location and number of the tumors. The distribution of different types of liver resection in patients with and without cirrhosis is shown in Table III. Compared with cirrhotic patients, a wider resection range was more common among non-cirrhotic patients.

R0, R1 and R2 resection was performed in 454 (34.6%), 591 (45.0%) and 215 (16.4%) patients, respectively; the remaining 52 (4.0%) patients only underwent exploratory laparotomy with biopsy due to unresectable disease (e.g., extensive intrahepatic metastases or peritoneal seeding). Compared with patients without cirrhosis, a significantly higher rate of R0 resection was achieved in patients with cirrhosis (Table III).

Survival of the entire cohort. The duration of survival was defined as the time from surgery to the date of death or the last follow-up, and the median follow-up period was 47 months (range, 1-93 months). The 1-, 3- and 5-year OS rates for the entire cohort were 57.0, 19.9 and 13.3%, respectively, with a median survival time (MST) of 14.0 months.

Survival of patients with and without cirrhosis. A significant difference in survival rates was observed between patients

Table II. Comparison of pathological characteristics between intrahepatic cholangiocarcinoma patients with and without cirrhosis.

Characteristics	With cirrhosis, n (%) (n=302)	Without cirrhosis, n (%) (n=1,010)	P-value
Tumor size (cm)			<0.001
Mean ± standard deviation	6.39±3.69	7.29±3.53	
Tumor number			0.225
Single	202 (66.9)	637 (63.1)	
Multiple	100 (33.1)	373 (36.9)	
Capsule formation	40 (13.2)	36 (3.6)	<0.001
Differentiation			
High or moderate	269 (89.1)	944 (93.5)	0.011
Poor	33 (10.9)	66 (6.5)	
Lymphatic metastasis	52 (17.2)	318 (31.5)	<0.001
Vascular invasion	92 (30.5)	111 (11.0)	<0.001
Perineural invasion	5 (1.7)	91 (9.0)	<0.001
Stage			<0.001
I-II	225 (74.5)	604 (59.8)	
III-IV	77 (25.5)	406 (40.2)	

Table III. Distribution of different types of liver resection in intrahepatic cholangiocarcinoma patients with and without cirrhosis.

Types of liver resection	With cirrhosis, n (%)	Without cirrhosis, n (%)	P-value
Surgical range	296	964	
Segmentectomy or local resection	90 (30.4)	160 (16.6)	<0.001
Bisegmentectomy	129 (43.6)	388 (40.2)	0.308
Hemihepatectomy	63 (21.3)	361 (37.4)	<0.001
Extended hemihepatectomy	14 (4.7)	55 (5.7)	0.519
Surgical margin status	302	1,010	
R0 resection	146 (48.3)	308 (30.5)	<0.001
R1 resection	113 (37.4)	478 (47.3)	0.002
R2 resection	37 (12.3)	178 (17.6)	0.027
Exploratory laparotomy	6 (2.0)	46 (4.6)	0.045

with and those without cirrhosis; the 1-, 3- and 5-year OS rates for patients with and without cirrhosis were 62.3, 24.1 and 14.7% (MST, 16.0 months), and 55.4, 18.7 and 13.0% (MST, 13.0 months), respectively (P<0.038, Fig. 1).

Univariate and multivariate analyses. The univariate analysis demonstrated that certain variables, including HBV infection, cirrhosis, presence of cholelithiasis, serum level of CA19-9 and/or CEA, tumor size, tumor number, capsule formation, LN metastasis, vascular invasion, perineural invasion and surgical margin status, were statistically significant prognostic factors affecting the survival of ICC patients (Table IV). Cox's regression multivariate analysis identified HBV infection and cirrhosis as independent favorable prognostic factors, while the presence of cholelithiasis, elevated CA19-9 and CEA levels, multiple tumors, lymphatic metastasis, vascular invasion and positive surgical margin status were independent unfavorable prognostic factors, with hazard ratios of 1.330, 1.726, 1.380, 1.297, 1.193 and 1.788, respectively (Table IV).

Discussion

ICC is a heterogeneous group of tumors, with different risk factors, biological behavior and clinicopathological characteristics and, consequently, different prognosis (1,2,6,15). HBV infection and cirrhosis are established risk factors for HCC (8,11), and several recent studies have suggested HBV infection may also be associated with the occurrence of ICC (12,13,18,19); however, the association between cirrhosis and the pathogenesis/prognosis of ICC remains unknown. The present study confirmed the earlier observation that cirrhosis is prevalent among patients with ICC in highly endemic areas (6), as it was observed in 23.0% of our patients, which is a markedly higher percentage compared with Western

Table IV. Univariate and multivariate analyses of variables associated with overall survival after surgery in 1,312 patients with intrahepatic cholangiocarcinoma.

Variables	N (%)	Median survival (months)	Univariate analysis (P-value)	Multivariate analysis	
				P-value	HR (95% CI)
Age (years)			0.795	-	-
≤60	920 (70.1)	14			
>60	392 (29.9)	14			
Gender			0.736	-	-
Male	896 (68.3)	14			
Female	416 (31.7)	13			
HBsAg			<0.001	<0.001	1.435 (1.248-1.649)
(-)	714 (54.4)	12			
(+)	598 (45.6)	19			
Cirrhosis			0.038	<0.001	1.367 (1.161-1.609)
No	1,010 (77.0)	13			
Yes	302 (23.0)	16			
Alcoholic			0.473	-	
No	1,122 (85.5)	14			
Yes	190 (14.5)	15			
Schistosomiasis			0.762	-	
No	1,241 (94.6)	14			
Yes	71 (5.4)	13			
Cholelithiasis			<0.001	<0.001	1.330 (1.145-1.545)
No	1,058 (80.6)	15			
Yes	254 (19.4)	10			
AFP elevation			0.675		
No	1,064 (81.1)	14			
Yes	248 (19.0)	14			
CA19-9 and/or CEA elevation			<0.001	<0.001	1.726 (1.520-1.959)
No	536 (40.9)	23			
Yes	776 (59.1)	11			
Tumor size (cm)			<0.001	0.105	-
≤5	464 (35.4)	20			
>5	848 (64.6)	12			
Tumor number			<0.001	<0.001	1.380 (1.212-1.571)
Single	839 (63.9)	18			
Multiple	473 (36.1)	10			
Capsule formation			<0.001	0.141	-
No	1,236 (94.2)	14			
Yes	76 (5.8)	25			
Lymph node metastasis			<0.001	0.001	1.297 (1.110-1.515)
No	942 (71.8)	18			
Yes	370 (28.2)	8			
Vascular invasion			0.010	0.036	1.193 (1.012-1.407)
No	1,109 (84.5)	14			
Yes	203 (15.5)	13			
Perineural invasion			0.001	0.235	-
No	1,216 (92.7)	14			
Yes	96 (7.3)	11			
Differentiation			0.836	-	-
High or moderate	1,213 (92.5)	14			
Poor	99 (7.5)	13			

Table IV. Continued.

Variables	N (%)	Median survival (months)	Univariate analysis (P-value)	Multivariate analysis P-value	HR (95% CI)
Surgical margin status			<0.001	<0.001	1.788 (1.612-1.984)
R0 resection	454 (34.6)	24			
R1 resection	591 (45.0)	14			
R2 resection	215 (16.4)	6			
Exploratory laparotomy	52 (4.0)	4			

AFP, α-fetoprotein; HBsAg, hepatitis B surface antigen; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; HR, hazard ratio; CI, confidence interval.

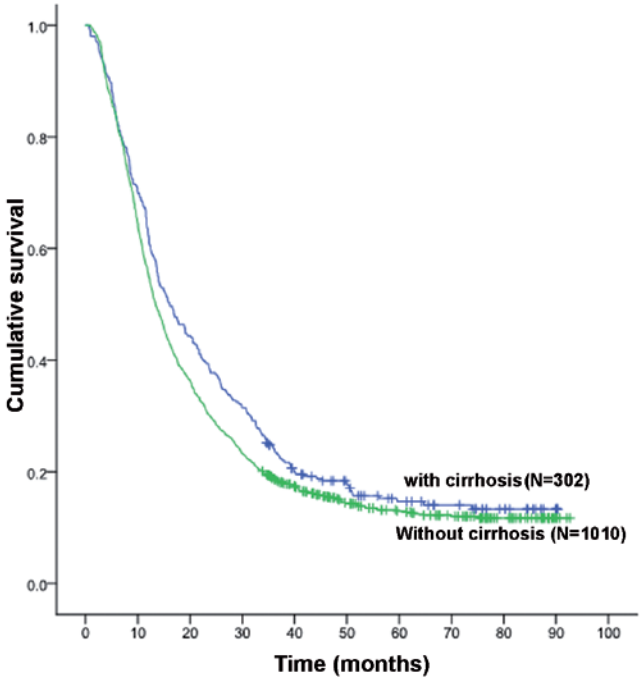

Figure 1. Overall survival (OS) in intrahepatic cholangiocarcinoma patients with and without cirrhosis: The 1-, 3- and 5-year OS rated for patients with cirrhosis were 62.3, 24.1 and 14.7%, respectively, which were significantly higher compared with the corresponding rates in patients without cirrhosis (55.4, 18.7 and 13.0%, respectively), with median survival times of 16.0 vs. 13.0 months, respectively (P<0.038).

countries (15). Cirrhosis is most likely associated with HBV infection in China (26), and 90.1% of cases with cirrhosis in the present series were seropositive for hepatitis B surface antigen, indicating HBV-related cirrhosis. Although the prevalence in our study may not prove a causal association between cirrhosis and ICC, as is the case with HCC, it indicates a correlation between the two. Patients with cirrhosis have a ~16-fold higher risk of HCC compared with inactive carriers (8). Therefore, future investigation should examine whether cirrhosis plays a synergistic role in ICC development in patients with HBV infection.

It is generally hypothesized that the prognosis of ICC is worse compared with that of HCC following surgical treatment (2,5,27). Complete surgical resection is the only curative treatment for ICC; however, similar to previous reports (2,6,7,25), the OS of this entire cohort indicated that the prognosis of ICC is dismal following surgical management, with an MST of only 14.0 months, as the disease is usually advanced at the time of diagnosis. There are several known factors affecting the prognosis of ICC after surgery, including surgical margin status, multiple tumors, LN metastasis and vascular invasion (2,6,7,25,28). In earlier studies on ICC, cirrhosis (21), unlike HBV infection (13,18,19), was shown to be an independent unfavorable prognostic factor for survival, but little is known on the underlying mechanism. However, the multivariate analysis in this series and our former study (20) revealed that cirrhosis was an independent favorable prognostic factor for survival of ICC patients following surgery. Different sample sizes may be the reason for the different results reported by these studies regarding the role of cirrhosis in ICC prognosis.

In the present study, all the patients with underlying liver disease had well-compensated liver function (Child A), which, in non-cirrhotic cases, should not significantly affect the extent of hepatectomy or postoperative morbidity and mortality. However, as reported by an earlier study on ICC (21), cirrhosis exerts a negative effect on major hepatectomy, and cirrhotic patients in our study tended to have a smaller resection range (Table III). Non-cirrhotic patients may be more amenable to resection due to a relatively better preserved liver function, as in HCC tumors (16,17). However, the R0 resection rate was significantly higher among cirrhotic patients (P<0.001), while the rates of non-curative resection [R1 (P=0.002) and R2 (P=0.027)] and exploratory laparotomy (P=0.045) were significantly higher among non-cirrhotic patients, which may be one of the reasons for the superior survival of ICC patients with cirrhosis. ICCs in non-cirrhotic patients tended to be larger, with a lower incidence of capsule formation, and at a more advanced stage at diagnosis compared with those in cirrhotic patients (Table II), which may be the reason for the better surgical margin status and survival in ICC patients with cirrhosis. ICC patients with cirrhosis exhibited a significantly better survival compared with those without cirrhosis (Fig. 1), which may not be attributed to early tumor detection. Although our data demonstrated that patients with cirrhosis had significantly smaller tumors compared with those without cirrhosis (Table I), tumor size was not found to be an independent prognostic factor for ICC patients. In the

present study, the presence of cholelithiasis, HBV infection, elevated CA19-9 and CEA levels, surgical margin status and certain pathological characteristics, such as multiple tumors, capsule formation, lymphatic metastasis and vascular invasion, were significantly associated with the presence of cirrhosis, but the associations were not causative, and multivariate analysis demonstrated that these factors together with cirrhosis were all independent prognostic factors for ICC (Table IV). The differences in the clinicopathological characteristics between ICC patients with and those without cirrhosis may be due to different underlying pathogenic mechanisms in the two groups of patients.

According to previous studies, the development of HCC in cirrhotic and non-cirrhotic livers may be underlined by distinct mechanisms (8,9), which has not been proven in ICC patients. In the present study, in the clinical setting, ICC patients with cirrhosis exhibited different and unique characteristics compared with patients without cirrhosis. The findings of this study suggested that ICC associated with cirrhosis may display a biological behavior similar to that of HCC and, thus, have a better prognosis. Although the etiology of ICC remains unclear, there is growing evidence suggesting that ICC associated with cirrhosis may be derived from the same hepatic progenitor cells as HCC (13,14,18,19) and, thus, behaves more like HCC, which is generally considered to have a more favorable prognosis compared with ICC (2,5,27,29). The observations of the present study indicate that ICC occurring in patients with cirrhosis may share a common carcinogenic process with HCC. Compared with non-cirrhotic patients, cirrhotic ICC patients were more likely younger and male, a profile resembling that of HCC patients (18,19). The formation of vascular tumor thrombi, one of pathological characteristics of HCC, was observed more often among ICC patients with cirrhosis compared with those without cirrhosis. In contrast to a previous study (21), LN metastasis and perineural invasion, which are typical pathological characteristics of adenocarcinoma, were less often found in ICC patients with cirrhosis compared with those without cirrhosis. AFP is often used as a tumor marker for HCC and, in the present study, a significantly higher number of cirrhotic ICC patients exhibited elevated serum AFP levels compared with non-cirrhotic patients, suggesting that the ICC cells may exhibit hepatocellular differentiation. These findings also suggest that ICC with cirrhosis and HCC may share a common carcinogenic process.

The present study had several limitations. First, a small number of patients with mild fibrosis or steatosis were included, which may have affected the findings; however, none of these patients had true cirrhosis and, therefore, were considered eligible for inclusion in the cohort of non-cirrhotic patients. Patients with HCV infection, a known inciting factor of hepatocarcinogenesis (12), were not included in the present study due to the small case series of HCV infection. A number of patients received non-radical resection and a considerable percentage of non-anatomical hepatectomies were included in this study, due to the advanced tumor stage at the time of diagnosis and the high incidence of chronic liver disease, such as HBV infection and cirrhosis, prevalent in China. Furthermore, although it included the largest case series of ICC patients, this study was retrospective in nature, which may be associated with certain limitations with regards to data selection.

In conclusion, cirrhosis is an independent favorable prognostic factor for survival of ICC patients, due to the distinct biological characteristics as well as the different pathogenic mechanism in this subgroup of patients. More emphasis should be placed on aggressive surgical treatment for ICC patients with cirrhosis, considering safety and better survival in this group. Non-cirrhotic patients may lack the typical 'field-defect' of a cirrhotic liver; however, these patients may harbor a molecular field defect that differs from that of a cirrhotic liver, leading to higher-risk pathological characteristics, lower resection rates and worse survival. Further investigation should be focused on the genomic profile of livers with and without cirrhosis in order to elucidate the different pathogenic mechanisms underlying the development of ICC, in order to design novel targeted treatments to improve the survival of ICC patients.

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