Risk Factors of Recurrence After Curative Resection of Hepatocellular Carcinoma in Taiwan

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Abstract: *Introduction:* The purpose of this study was to explore the potential risk factors of hepatocellular carcinoma (HCC) recurrence after curative resection of primary HCC. *Methods:* This was a hospital-based retrospective cohort study. The authors analyzed the medical records of all the subjects with HCC initially treated by hepatic resection at a medical center in Taiwan from 1995 to 2006. In all, 222 subjects were enrolled in this study. The total observational period was 3 years. *Results:* There were 172 men (77.5%) and 50 women (22.5%). The mean age was 57.0 ± 13.7 years (range, 15–79 years). Among 222 subjects, the overall recurrence rates were 28.8% (64/222), 42.3% (94/222) and 47.7% (106/222) at 1, 2 and 3 years, respectively. Multivariate logistic regression analysis exhibited that tumor size ≥5 cm [odds ratio (OR) = 2.31, 95% confidence interval (CI) = 1.27–4.17], liver cirrhosis (OR = 2.11, 95% CI = 1.18–3.79) and preoperative aspartate aminotransferase level ≥34 IU/L (OR = 2.02, 95% CI = 1.01–4.04) were independent risk factors of HCC recurrence. *Conclusion:* Patients who have larger tumor size, liver cirrhosis and higher preoperative aspartate aminotransferase level should be carefully followed up because they are at high risk of HCC recurrence postoperatively.

Key Indexing Terms: Aspartate aminotransferase; Cirrhosis; Hepatocellular carcinoma; Recurrence; Tumor size. **[Am J Med Sci 2011; 341(4):301–304.]**

To date, treatment modalities for hepatocellular carcinoma (HCC) include surgical resection, percutaneous radiofrequency ablation, percutaneous ethanol injection, transarterial embolization and liver transplantation. However, HCC recurrence is frequently detected after ablation therapy for primary HCC. The cumulative recurrence rates after ablation therapy are around 37.0% to 59.7% at 1 year and 71.6% to 76.5% at 3 years, respectively,[1,2] depending on the underlying causes, the initial treatment modalities, the follow-up duration and the population studied.

Although the real pathogenesis of HCC recurrence after ablation therapy remains unclear, the risk factors of HCC recurrence include the larger tumor size, the smaller ablative/resection margin, the presence of vascular invasion, multiple HCC nodules, histologic classification, pretreatment high serum alpha-fetoprotein (AFP) level, pretreatment low platelet count, pretreatment low serum albumin level and visceral fat accumulation.[1–10] Therefore, close observation to detect any early recurrence sign in patients with these mentioned risk factors is needed.

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Submitted June 21, 2010; accepted in revised form September 30, 2010. The authors disclose no conflicts of interest.

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HCC ranked the second leading cause of cancer death in Taiwan in 2009.[11] It accounted for approximately 7809 deaths in 2007, 7651 deaths in 2008 and 7759 death in 2009.[11] At present, although some studies have reported the risk factors of HCC in Taiwan,[2–5] for establishing the newer evidence, we conducted this retrospective cohort study to explore the potential risk factors of HCC recurrence.

MATERIALS AND METHODS

Study Population and Inclusion Criteria

This was a hospital-based retrospective cohort study. We analyzed the medical records of all the subjects diagnosed as having initial HCC at a medical center located at Taichung city in Taiwan from 1995 to 2006. The institutional review board of this medical center approved this retrospective study.

The inclusion criteria for this study were as follows: (i) subjects who underwent hepatic resection of primary tumors and pathologic reports confirmed as having HCC; (ii) subjects who did not have extrahepatic metastasis or vessel invasion based on imaging; and (iii) subjects who were considered as having complete curative response 1 month after hepatic resection of primary tumors.[5,12] All subjects underwent computed tomography or abdominal ultrasonography at 1 month after hepatic resection of primary tumors to assess the therapeutic effects. No focal lesion in the liver or in the other organs was regarded as complete curative response. In all, 222 subjects meeting the inclusion criteria were enrolled in this study. The total observational period was 3 years.

Serum Data

The preoperative serum data including aspartate aminotransferase (AST), alanine aminotransferase, albumin, total

TABLE 1. Basic characteristics of the study population

Variable	
Sex, n (%)	
Men	172 (77.5)
Women	50 (22.5)
Age (yr), mean ± SD	57.0 ± 13.7
AST (IU/L), mean ± SD	61.3 ± 48.9
ALT (IU/L), mean ± SD	58.5 ± 41.2
Total bilirubin (mg/dL), mean ± SD	1.0 ± 0.9
Albumin (g/dL), mean ± SD	3.6 ± 0.5
AFP (ng/mL), mean ± SD	6229.5 ± 50016.0
Platelet count ($\times 10^3/mm^3$), mean ± SD	185.9 ± 99.3
Prothrombin time (sec), mean ± SD	12.5 ± 1.4
Child-Pugh score (mean ± SD)	5.6 ± 0.8

AST, aspartate aminotransferase; ALT, alanine aminotransferase; AFP, alpha-fetoprotein; SD, standard deviation.

TABLE 2. Factors related to recurrence of HCC after hepatic resection by univariate analysis

Variable	Nonrecurrence (n = 116)	Recurrence (n = 106)	*P*
Age (yr), mean ± SD	56.9 ± 13.6	57.1 ± 13.8	0.891
Prothrombin time (sec), mean ± SD	12.5 ± 1.4	12.5 ± 1.3	0.837
Child-Pugh score (mean ± SD)	5.5 ± 0.9	5.6 ± 0.8	0.504
Sex, n (%)			0.547
Men	88 (75.9)	84 (79.2)	
Women	28 (24.1)	22 (20.8)	
AST (IU/L), n (%)[a]			0.014
<34	34 (29.3)	16 (15.4)	
≥34	82 (70.7)	88 (84.6)	
ALT (IU/L), n (%)[a]			0.972
<40	46 (39.7)	41 (39.4)	
≥40	70 (60.3)	63 (60.6)	
Total bilirubin (mg/dL), n (%)[a]			0.400
<1.3	96 (83.5)	91 (87.5)	
≥1.3	19 (16.5)	13 (12.5)	
Albumin (g/dL), n (%)[a]			0.071
≥3.8	58 (50.4)	39 (38.2)	
<3.8	57 (49.6)	63 (61.8)	
AFP (ng/mL), n (%)[a]			0.041
<9	52 (45.6)	33 (32.0)	
≥9	62 (54.4)	70 (68.0)	
Platelet count, n (%)[a]			0.618
≥100,000/mm^3	100 (86.2)	88 (83.8)	
<100,000/mm^3	16 (13.8)	17 (16.2)	
Hepatitis status, n (%)			0.202
HBsAg (−) and anti-HCV (−)	23 (19.8)	15 (14.2)	
HBsAg (+) and anti-HCV (−)	53 (45.7)	40 (37.7)	
HBsAg (−) and anti-HCV (+)	33 (28.4)	40 (37.7)	
HBsAg (+) and anti-HCV (+)	7 (6.0)	11 (10.4)	
Ascites, n (%)			0.427
No	112 (96.6)	100 (94.3)	
Yes	4 (3.4)	6 (5.7)	
Liver cirrhosis, n (%)			0.012
No	61 (52.6)	38 (35.8)	
Yes	55 (47.4)	68 (64.2)	
Tumor nodule, n (%)			0.215
Solitary	103 (88.8)	88 (83.0)	
≥2	13 (11.2)	18 (17.0)	
Tumor size (cm), n (%)			0.009
<5	81 (69.8)	56 (52.8)	
≥5	35 (30.2)	50 (47.2)	
Section margin (cm), n (%)[a]			0.565
≥1	40 (48.2)	37 (52.9)	
<1	43 (51.8)	33 (47.1)	
Pathological grade, n (%)			0.973
Grade 1	2 (1.7)	2 (1.9)	
Grade 2	54 (46.6)	46 (43.4)	
Grade 3	56 (48.3)	54 (50.9)	
Grade 4	4 (3.4)	4 (3.8)	
CLIP score, n (%)[a]			0.173
0	70 (60.3)	49 (46.7)	
1	25 (21.6)	23 (21.9)	
2	12 (10.3)	19 (18.1)	
3	7 (6.0)	9 (8.6)	
4	2 (1.7)	5 (4.8)	
5	0 (0)	0 (0)	

[a] Imprecise summation of total subjects was because of missing data.
AST, aspartate aminotransferase; ALT, alanine aminotransferase; AFP, alpha-fetoprotein; HBsAg, hepatitis B virus surface antigen; HCV, hepatitis C virus; CLIP, Cancer of the Liver Italian Program; SD, standard deviation.

bilirubin, AFP, platelet count, prothrombin time, hepatitis B virus surface antigen and hepatitis C antibody were collected. Child–Pugh score, HCC Pathological grade[13] and Cancer of the Liver Italian Program score[14] were also measured. Liver cirrhosis was diagnosed by pathologic finding. Ascites was detected by abdominal ultrasonography. All subjects underwent routine abdominal ultrasonography, liver function tests and serum AFP at 3-month intervals after hepatic resection of primary tumors. When suspicious findings on ultrasonography or abnormal serum data were detected, computed tomography was arranged to confirm recurrent HCC.

Statistical Analysis

Statistical analysis was performed by SPSS (Taiwan Version 12.0; Sinter Information, Taipei, Taiwan). The Student *t* test was performed for continuous variables, and the χ^2 test was performed for qualitative variables. The relative risks were estimated by adjusted odds ratio (OR) and 95% confidence interval (CI) using a multivariate logistic regression model. Cumulative recurrence rates were calculated by the Kaplan–Meier method during follow-up period, and differences were compared by log-lank test. A *P*-value of <0.05 was considered statistically significant.

RESULTS

Basic Characteristics of the Study Population

The basic characteristics were shown in Table 1. There were 172 men (77.5%) and 50 women (22.5%). The mean age was 57.0 ± 13.7 years (range, 15–79 years).

Related Factors of HCC Recurrence by Univariate Analysis

Among 222 subjects, the overall recurrence rates were 28.8% (64/222), 42.3% (94/222) and 47.7% (106/222) at 1, 2 and 3 years, respectively. By using the Student *t* test and χ^2 test, the statistically related factors of HCC recurrence were found to be preoperative AST level ($P = 0.014$), preoperative AFP level ($P = 0.041$), liver cirrhosis ($P = 0.012$) and tumor size ($P = 0.009$; Table 2).

TABLE 3. Factors related to HCC recurrence by multivariate analysis

Variable	Odds ratio (95% CI)
Tumor size (cm) (≥5 vs. <5)	2.31 (1.27–4.17)[a]
Liver cirrhosis (yes vs. no)	2.11 (1.18–3.79)[b]
AST (IU/L) (≥34 vs. <34)	2.02 (1.01–4.04)[b]
AFP (ng/mL) (≥9 vs. <9)	1.59 (0.89–2.85)

[a] $P < 0.01$.
[b] $P < 0.05$.
AST, aspartate aminotransferase; AFP, alpha-fetoprotein; CI, confidence interval.

Risk Factors of HCC Recurrence by Multivariate Logistic Regression

Only the statistically related factors identified in univariate analysis were further analyzed. After controlling for the other covariates, multivariate logistic regression analysis exhibited that the OR of HCC recurrence was 2.31 (95% CI = 1.27–4.17, $P = 0.006$) for subjects with tumor size ≥5 cm, compared with subjects with tumor size <5 cm. The OR of HCC recurrence was 2.11 (95% CI = 1.18–3.79, $P = 0.012$) for subjects with liver cirrhosis, compared with subjects without liver cirrhosis. The OR of HCC recurrence was 2.02 (95% CI = 1.01–4.04, $P = 0.047$) for subjects with preoperative AST level ≥34 IU/L, compared with subjects with preoperative AST level <34 IU/L (Table 3).

Cumulative Recurrence Rates of HCC

We further analyzed the cumulative recurrence rates of HCC by tumor size, liver cirrhosis and preoperative AST level. The recurrence rates for subjects with tumor size ≥5 cm and <5 cm were 43.5% and 19.7% at 1 year ($P < 0.0001$), 52.9% and 35.8% at 2 years ($P = 0.0016$) and 58.8% and 40.9% at 3 years ($P = 0.0012$), respectively. The recurrence rates for subjects with liver cirrhosis and without cirrhosis were 31.7% and 25.3% at 1 year ($P = 0.3994$), 49.6% and 33.3% at 2 years ($P = 0.0377$) and 55.3% and 38.4% at 3 years ($P = 0.0273$), respectively. The recurrence rates for subjects with preoperative AST level ≥34 IU/L and <34 IU/L were 33.5% and 12.0% at 1 year ($P = 0.005$), 47.1% and 24.0% at 2 years ($P = 0.0048$) 51.8% and 32.0% at 3 years ($P = 0.0111$), respectively.

DISCUSSION

Although not novel, our study made a major finding that larger tumor size, liver cirrhosis and higher preoperative AST level are independent risk factors of HCC recurrence. In this study, we found that a 2.3-fold risk of HCC recurrence in subjects with tumor size ≥5 cm is revealed when compared with tumor size <5 cm. In the study by Jwo et al,[3] they found tumor size greater than 5 cm was also a risk factor of HCC recurrence. In the study by Lam et al,[6] they found tumor size >2.5 cm was the only independent risk factor of local recurrence. To the best of our knowledge, there is not a consensus about what size of tumor is risky for HCC recurrence, but we think the larger the tumor, the riskier for HCC recurrence.

In this study, we found that a 2.1-fold risk of HCC recurrence in subjects with liver cirrhosis is revealed when compared with subjects without liver cirrhosis. The former studies have also proven that liver cirrhosis is a risk factor of HCC recurrence.[15,16] In the study by Poon et al,[17] they found liver cirrhosis is the only significant risk factor for late recurrence (>1 year; risk ratio = 2.378, $P = 0.018$). Cirrhosis is known as a precancerous lesion. The previous studies have reported that the high risk for developing HCC in cirrhotic liver was related to high hepatocellular proliferation, presumably by increased rate of random mutations and promotion.[18,19]

In this study, the risk of HCC recurrence was increased by 2-fold in subjects with preoperative AST level ≥34 IU/L, when compared with subjects with preoperative AST level <34 IU/L. In the study by Kubo et al,[20] the risk of HCC recurrence was increased by 1.7-fold in subjects with AST level >40 IU/L (95% CI = 1.05–2.84, $P = 0.03$). In the study by Fuke et al,[21] the risk of HCC distant recurrence was increased by 4.3-fold in subjects with AST level >60 IU/L (95% CI = 1.918–9.721, $P = 0.0004$). These above findings further confirm that the underlying inflammatory state of liver has greater effect on HCC recurrence.[20,21]

Some limitations should be mentioned. First, this was a population-based study. These data could not be representative of all people in Taiwan. Second, the follow-up period was short. Some potential risk factors might not be revealed during the short time. Third, the prognostic importance of microscopic vascular invasion was not included in this study. A long-term prospective study with a more representative group of subjects is needed to confirm our data.

CONCLUSION

This study has shown that tumor size ≥5 cm, liver cirrhosis and preoperative AST level ≥34 IU/L are the risk factors of HCC recurrence. That is, patients who have larger tumor size, liver cirrhosis and higher preoperative AST level should receive close surveillance because they are at high risk of HCC recurrence postoperatively. We hope that this study can provide the basic information about HCC recurrence in Taiwan.

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