Predictors of Long-term Survival in Hepatocellular Carcinomas: A Longitudinal Follow-up of 108 Patients with Small Tumors

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Abstract. *Aim: Locoregional treatment [including percutaneous ethanol injection (PEI) therapy and transcatheter arterial chemoembolization (TACE)] provides an alternative treatment for early-diagnosed hepatocellular carcinoma (HCC). However, the long-term survival of patients after locoregional treatments remains unclear. Patients and Methods: A total of 108 patients with small HCC not indicated for surgical hepatic resection were recruited between 1991 and 1999. All patients received first treatment with PEI therapy alone or combined with TACE. We followed-up these patients until the end of 2007. Clinical attributes and biological markers in association with long-term survival were collected. Significant predictors were identified by using proportional hazards regression model. Results: The overall 1-, 3-, 5-, and 10-year cumulative survival of patients with HCC (<5 cm) were 88.8%, 59.4%, 29.4%, and 12.3%, respectively. Child-Pugh status, type of tumor (solitary or multiple), levels of pre-treatment aspartate aminotransferase (AST), and treatment modality were significantly associated with long-term survival after adjustment for age and gender. Child-Pugh B (hazard ration, HR=1.98, 95% confidence interval, CI=1.08-3.60) and higher level of pre-treatment AST (HR=1.91, 95% CI=1.18-3.08) were the two most significant predictors for risk of death from HCC-after adjusting for treatment modality and type of tumor. Conclusion: Child-Pugh score and AST level were demonstrated as the two major predictors for long-term survival in patients with small HCC not indicated for surgical treatment who underwent PEI-alone or combined with TACE. Clinical weights from Child-Pugh score and AST level are very informative for risk stratification and clinical surveillance of patients with small HCC treated by PEI-alone or combined with TACE.*

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Key Words: Hepatocellular carcinoma, percutaneous ethanol injection, survival, transcatheter arterial chemoembolization, Child-Pugh score, aspartate aminotransferase.

Hepatocellular carcinoma (HCC) accounts for approximately half a million deaths annually worldwide (1). Surveillance of HCC among high-risk populations and early detection strategies have led to an increase in the number of small HCC amenable to curative treatment (2, 3). Surgical resection is a treatment choice for small HCC and the 5-year survival rate after resection is above 50% (4).

The indication for surgical resection of HCC, however, is sometimes limited because many patients with HCC have severe liver dysfunction due to liver cirrhosis, despite an early diagnosis of HCC (5). Liver transplantation is a potentially curative treatment for patients with HCC with decompensated cirrhosis (6). However, there is a shortage of liver donors in Asian countries, particularly Taiwan, due to a culture and social norm with a somewhat negative attitude toward transplantation.

Locoregional treatment, including percutaneous ethanol injection (PEI) therapy and transcatheter arterial chemoembolization (TACE), is an alternative option for treatment of small HCC in patients unsuitable for surgical intervention or liver transplantation (7). Despite the wide range of treatments for small HCC, the long-term survival rate and relevant predictors among patients with small HCC remains unclear.

Previously, we conducted a longitudinal follow-up to assess the hazard rate of death from HCC after treatment (8). It was, therefore, possible to extend the follow-up time to estimate the long-term survival rate of patients with small HCC not indicated for surgical intervention and identify the significant clinical predictive factors responsible for the prognosis of death from HCC.

Patients and Methods

Between January 1991 and December 1999, a total of 108 patients with small (<5 cm) HCC unsuitable for surgical hepatic resection at one medical center in Taipei, Taiwan, were recruited under approval by the ethic committee in compliance with the Helsinki Declaration (8). This study was authorized and supervised by the Department of Gastroenterology, Shin-Kong Wu Ho-Su Memorial Hospital and participants agreed to provide information after instruction given to them by a senior gastroenterologist (CSL). All enrolled patients had liver cirrhosis and were unsuitable for surgical hepatic resection because of liver dysfunction, presence of lesions in locations not amenable to hepatic resection, or coexistence of other diseases. The details of this study have been described in full elsewhere (8). In brief, the diagnosis of HCC was confirmed by ultrasound (US)-guided fine-needle biopsy of the lesion in 35 patients; focal hepatic nodule(s) with typical images of HCC on US, computerized tomography (CT), angiography combined with elevated α fetoprotein (AFP) level above 200 ng/ml in 21 patients; focal hepatic nodule(s) with typical images of HCC on US and CT combined with hypervascular tumor stains on angiography in 46 patients; focal hepatic nodule(s) without typical images of HCC on US, CT, or angiography presenting with progression of tumor in six patients. The number of tumor nodules and absence of portal vein thrombosis were confirmed on the basis of US and CT scan findings. Tumor size in diameter was rated by US.

Criteria for locoregional treatment included: single, nodular HCC smaller than 5 cm or multiple (up to four) nodular HCC lesions less than 5 cm each; no portal vein thrombosis or extrahepatic metastases; cirrhosis classified as Child-Pugh A or B; absence of any symptoms related to bleeding, and a prothrombin time (PT) less than 16 seconds with platelet count higher than 40,000/μl.

PEI was performed by US-guided needle insertion and alcohol injection with multisession. The total amount of alcohol injected varied by tumor size. Estimated appropriate volume of injected ethanol for each tumor was calculated by the formula $V=(4/3)\pi r^3$, which V (in ml) was the tumor volume and r (in cm) was the radius of the tumor. In each session, a total volume of ethanol more than twice that of tumor volume was injected to achieve complete necrosis of the tumor. PEI was performed two or three times a week, depending on patient's tolerance and until the ethanol distributed throughout the tumor. After the PEI cycle, patients were examined by US and CT at one-month intervals. Levels of AFP were also measured. If a viable tumor was found, the administration of PEI was repeated. If no residual tumor was found, the patients were subject to periodical monitoring with AFP measurement and sonography at three-month intervals and CT scan at six-month intervals. By linking data with Taiwan Mortality Registry up to 2007, data on date of death and cause of death were collected for the subsequent survival analysis.

Statistical analysis. Cumulative survival rates of HCC cases were estimated by using the Kaplan-Meier method. The differences of cumulative survival rates between groups were compared by using the log-rank test. The proportional hazards regression model was used to assess the risk of HCC death for identifying the significant predictors responsible for the prognosis of HCC death. Clinical weights (regression coefficients, βs) and the value of predictors (Xs) were summed to derive a sickness score ($\beta_1X_1+\beta_2X_2+...+\beta_pX_p$). To render the range between 0 and 100, the original sickness score was multiplied by 37 and the baseline score of 27 added arbitrarily for each scenario. The predicted long-term survival rate was calculated by using the significant predictors identified in the multivariable proportional hazards regression model. A *p*-value less than 0.05 was considered to be statistically significant.

Results

There were 108 patients enrolled in this study, including 38 females and 70 males with an average age of 61±9.4 (SD) years. A total of 81 deaths from HCC were confirmed after follow-up until 31st Dec 2007. The mean follow-up time was approximately 3.26 years. Table I also shows competing causes of death for another 18 patients. Liver cirrhosis accounted for 67% of causes of death other than HCC. Only nine patients remained alive up to at least eight years of follow-up. The clinical descriptions for these nine patients are provided in Table II. These patients' HCCs were all small in size (<3 cm). Only one patient (patient 1) had a HCC over 2 cm in size. These patients also had early-stage liver cirrhosis, except for patient 8 with Child-Pugh score B. Six patients received PEI therapy alone and the remaining three patients were treated with PEI combined transcatheter arterial chemoembolization (TACE) treatment. The three patients who received PEI combined with TACE treatment and are still alive are all less than 61 years old (the mean age of this study cohort).

The overall 1-, 3-, 5-, and 10-year cumulative survival rates of patients with HCC (<5 cm) treated by PEI or PEI combined with TACE were 88.8%, 59.4%, 29.4%, and 12.3%, respectively.

Table III shows the demographic and clinical characteristics of 108 patients and the 1-, 3-, 5-, and 10-year cumulative survival rates stratified by relevant demographic and clinical characteristics. Among all of the variables that were evaluated with the Kaplan–Meier method, Child-Pugh score, type of tumor (solitary or multiple), level of aspartate aminotransferase (AST), and treatment modality (PEI-alone or PEI combined with TACE) were statistically significantly

Table I. *Number of patients with small hepatocellular carcinoma (HCC) stratified by cause of death, and their corresponding cause of death and time of follow-up.*

	No.	Follow-up time (years)	Notes
Overall	108	3.90±2.98	
HCC death	81	3.26±2.17	
Other cause of death	18	3.31±2.03	
Other cancer	3	3.64±1.10	Stomach cancer, n=1; colorectal cancer, n=1; Lung cancer, n=1
Liver cirrhosis	12	2.79±2.19	
Other cause	3	5.02±1.16	Stroke, n=2; shock without trauma, n=1
Alive	9	10.86 ±1.94	

Table II. *Clinical description of the nine patients alive after at least eight years of follow-up.*

Patient No.	Age (years)	Gender	Hepatitis	Treatment	Size (cm)	Type of tumor	CP	AFP (ng/ml)	AST (IU/l)	ALT (IU/l)	Total bilirubin (mg/dl)	Albumin (g/dl)	PT (s.)	Survival time (years)
1	43	M	B	PEI+TACE	2.5	Solitary	A	15.90	19	20	0.9	4.2	13.1	10.37
2	58	F	B	PEI+TACE	1.2	Solitary	A	7115.14	24	18	0.7	3.5	13.0	11.80
3	78	F	B	PEI	0.8	Solitary	A	3.70	53	69	0.7	4.1	12.2	10.34
4	69	F	C	PEI	1.1	Solitary	A	30.03	128	139	0.8	4.2	13.0	13.22
5	37	M	B	PEI	2.0	Solitary	A	3.01	33	46	0.8	5.2	11.3	14.12
6	31	F	C	PEI	1.3	Solitary	A	11.85	107	91	0.9	3.1	11.8	9.27
7	57	M	B	PEI	1.2	Solitary	A	248.42	26	20	0.6	3.5	11.9	11.32
8	57	F	C	PEI+TACE	2.0	Solitary	B	83.71	380	249	2.0	3.1	13.9	8.77
9	46	M	B	PEI	2.0	Solitary	A	13.80	34	37	0.9	4.9	12.3	8.54

AFP: α Fetoprotein; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CP: Child-Pugh; F: female; M: male; PEI: percutaneous ethanol injection; PT: prothrombin time; TACE: transcatheter arterial chemoembolization.

associated with long-term survival (Figure 1). However, gender, age, the etiology of liver cirrhosis (hepatitis B or hepatitis C), tumor size, AFP levels, and alanine aminotransferase (ALT) levels were not statistically significantly associated with long-term survival of HCC.

The 1-, 3-, 5-, and 10-year survival rates were 93.0%, 66.2%, 34.8%, and 14.0%, respectively, in 84 patients with Child-Pugh A cirrhosis. The corresponding rates in 24 patients with Child-Pugh B were 73.9%, 31.9%, 6.4%, and 0%, respectively. A significant association between Child-Pugh status and risk for death from HCC was noted ($p<0.001$). Cumulative survival rates for patients with multiple HCCs at 1, 3, 5, and 10 years after treatment were 72.7%, 31.5%, 0%, and 0%, respectively, whereas those for patients with solitary tumors were 90.6%, 62.5%, 32.8%, and 13.7%, respectively. Patients with solitary HCC had statistically significantly more favorable long-term survival than those with multiple tumors ($p=0.01$).

As far as treatment modality is concerned, patients undergoing PEI treatment alone had a significantly better prognosis than those undergoing PEI combined with TACE ($p=0.028$). Cumulative survival rates at 1, 3, 5, and 10 years after treatment with PEI alone were 95.6%, 72.1%, 36.7%, and 19.8%, respectively, while those for patients with PEI combined with TACE treatment were 83.9%, 50.3%, 23.9%, and 6.4%, respectively.

In contrast to ALT, we observed a significant association between pre-treatment AST levels and survival rate. Survival rates for patients with a level of AST >56 IU/l were significantly lower than for those with a lower level of AST (81.3%, 47.9%, 19.1%, and 8.5% vs. 96.3%, 70.9%, 39.9%, and 16.9% at 1, 3, 5 and 10 years, respectively. The overall difference was statistically significant ($p=0.009$).

In univariate analysis of the proportional hazards regression model, we found that Child-Pugh status, type of tumor, level of AST, and treatment modality were significantly predictive of the risk for death from HCC. Although age and gender were not significant in the univariate analysis, these two factors were still important potential confounding factors for survival for patients with HCC, and therefore were still retained in the multivariable analysis. The results showed that Child-Pugh status, type of tumor, level of AST and treatment modality were significant prognostic factors in association with the risk for HCC death (Table IV). The cumulative survival rates in patients with Child-Pugh B were significantly poorer than those with Child-Pugh A [hazard ratio (HR)=2.68, 95% confidence

Table III. *Cumulative survival of patients with small hepatocellular carcinomas stratified by demographic and clinical variables.*

Variable	No. of deaths/no. of patients	Cumulative survival rate (%) 1-Year	3-Year	5-Year	10-Year	*p*-Value
Total	81/108	88.8	59.4	29.4	12.3	
Gender						0.260
Male	53/70	87.0	56.1	28.7	8.4	
Female	28/38	92.1	65.3	30.9	19.6	
Age, years						0.715
<55	22/29	89.7	69.0	31.0	18.6	
55-64	35/44	88.5	54.8	28.5	8.5	
≥65	24/35	88.4	57.0	29.3	12.2	
HBsAg						0.491
Positive	36/48	85.3	63.0	33.9	15.1	
Negative	45/60	91.6	56.7	25.7	8.7	
Anti-HCV						0.729
Positive	40/51	90.2	61.6	27.1	7.4	
Negative	41/57	87.5	57.5	31.6	16.0	
Liver dysfunction						<0.001
Child-Pugh A	63/84	93.0	66.2	34.8	14.0	
Child-Pugh B	18/24	73.9	31.9	6.4	0	
Level of AFP						0.404
<200 ng/ml	56/78	92.2	64.7	29.7	12.8	
≥200 ng/ml	25/30	80.0	46.7	28.3	9.4	
Type of tumor						0.010
Solitary	71/97	90.6	62.5	32.8	13.7	
Multiple	10/11	72.7	31.5	0	0	
Tumor size						0.159
<2 cm	22/33	87.5	71.2	38.6	22.1	
2-5 cm	49/64	92.2	58.2	29.9	8.2	
Level of AST						0.009
Low (≤56 IU/l)	37/54	96.3	70.9	39.9	16.9	
High (>56 IU/l)	44/54	81.3	47.9	19.1	8.5	
Level of ALT						0.639
Low (≤40 IU/l)	37/53	90.5	62.3	30.9	13.9	
High (>40 IU/l)	44/55	87.2	56.7	28.0	10.9	
Treatment modality						0.028
PEI	31/46	95.6	72.1	36.7	19.8	
PEI+TACE	50/62	83.9	50.3	23.9	6.4	

AFP: α Fetoprotein; ALT: alanine aminotransferase; Anti-HCV: anti-hepatitis C antibody; AST: aspartate aminotransferase; HBsAg: hepaptitis B surface antigen; PEI: percutaneous ethanol injection; TACE: transcatheter arterial chemoembolization.

interval (CI)=1.52-4.73]. Patients with multiple tumors were at greater risk for death from HCC than those with solitary tumors (HR=2.53, 95% CI=1.26-5.08). A higher level of pre-treatment AST significantly increased the risk for death from HCC (HR=1.94, 95% CI=1.23-3.07). However, PEI treatment alone conferred better prognosis than PEI combined with TACE (HR=0.6, 95% CI=0.38-0.96). In multivariable regression analysis with the incorporation of age and gender, and adjusting these four clinical factors for each other, Child-Pugh status and level of pre-treatment AST remained statistically significant for an elevated risk of death from HCC.

Figure 2 demonstrates the cumulative survival rates according to treatment modality, type of tumor, level of AST and Child-Pugh classification. Patients with solitary tumor, Child-Pugh A, lower level of pre-treatment AST, and PEI treatment alone had the highest survival rate, at approximately 50% for 5-year survival rate and 40% for 10-year survival rate. The Child-Pugh B group of patients with multiple tumors and higher level of pretreatment AST who underwent PEI combined with TACE treatment had the lowest survival rates with 5-year survival less than 4% and no 10-year survivors

Table V lists the sickness score by tertile distribution to classify small HCC treated by PEI and PEI combined with TACE into patients of high-risk (sickness score higher than 50), intermediate-risk (sickness score between 30 and 50), and low-risk (sickness score less than 30) groups. Five-year risk of dying from HCC for the three cases illustrated in Table V was 99.7% for the high-risk group, 76.6% for the intermediate-risk group, and 52.8% for the low-risk group.

Discussion

PEI therapy with sonographic guidance, which appears to be widely applicable to small HCCs was developed in the early 1980s (9, 10). PEI had a place in the treatment strategy of HCC, generally as a second choice when surgical intervention was not adequate for patients with early-stage tumors (11). The survival rates of patients with small HCCs were comparable between post-surgery and post-PEI groups (12-14). Compatible with a previous study (15), our study showed that the 5-year survival rate among patients with solitary tumors, Child-Pugh A and low level of pre-treatment AST, and who received PEI treatment alone, was approximately 50%. An encouraging result by our study was that the long-term 10-year survival rate reached 30%.

TACE is recommended for intermediate-stage HCC according to the American Association for the Study of Liver Disease guidelines (4). The capability of TACE to induce extensive tumor necrosis is still debated, and this technique is considered to be a noncurative modality. A recent study using the pathological specimens of patients with small HCCs (<5 cm) after liver transplantation to evaluate the efficacy of TACE performed before liver transplantation showed that the mean histological necrosis level was 64.7% and the complete tumor necrosis rate was about 42.6% (16). Moreover, single tumor showed a higher degree of mean tumor necrosis (86.1%) than multiple tumors (57.1%). Incomplete necrosis might increase the rate of tumor recurrence and reduce the long-term survival. Our present analysis showed coherent results among patients with small HCCs (<5 cm). Patients treated by PEI combined with TACE had poorer long-term prognosis than patients treated with PEI alone. Furthermore, patients with multiple tumors also had lower long-term survival rate than patients with solitary tumor.

Table IV. *Univariate and multivariate analysis of risk predictors of hepatocellular carcinoma-related death included in the Cox regression models.*

	Univariate			Multivariable					
				Model 1†			Model 2‡		
Variable	Hazard ratio	95% CI	*p*-Value	Adjusted hazard ratio	95% CI	*p*-Value	Adjusted hazard ratio	95% CI	*p*-Value
Liver dysfunction									
Child-Pugh A	1			1			1		
Child-Pugh B	2.57	1.50-4.41	<0.001	2.68	1.52-4.73	<0.001	1.98	1.08-3.60	0.026
Type of tumor									
Solitary	1			1			1		
Multiple	2.37	1.21-4.64	0.012	2.53	1.26-5.08	0.009	1.65	0.78-3.49	0.194
Level of AST									
Low ≤56 IU/l	1			1			1		
High >56 IU/l	1.78	1.15-2.77	0.010	1.94	1.23-3.07	0.005	1.91	1.18-3.08	0.008
Treatment modality									
PEI	0.61	0.38-0.95	0.030	0.60	0.38-0.96	0.032	0.64	0.39-1.04	0.070
PEI+TACE	1			1			1		

AST: Aspartate aminotransferase; CI: confidence interval; PEI: percutaneous ethanol injection; TACE: transcatheter arterial chemoembolization. †Adjusted for age and gender; ‡adjusted for age, gender, liver dysfunction, type of tumor, level of AST and treatment modality accordingly.

Child-Pugh score is known to correlate with the severity of liver cirrhosis and is independently predict the mortality risk. Previous studies found that the Child–Pugh score is the major predictor of prognosis in patients with cirrhosis and HCC who underwent treatment with PEI (15, 17). Livraghi *et al*. reported that the 5-year survival rates of patients with single HCC (<5 cm) with Child-Pugh score A and B were 47 and 29%, respectively (15). Our study also demonstrated compatible results. Patients with Child-Pugh B had significantly poorer prognosis than patients with Child-Pugh A (HR=2.68, 95% CI=1.52-4.73).

Interestingly, our present study found that higher level of AST conferred significantly poor prognosis. These findings were also revealed in our previous study with shorter follow-up time (18). The reason for this finding is not clear. Several studies have shown that an AST/ALT ratio of unity or higher has good specificity and sensitivity for the diagnosis of cirrhosis (19-23). The AST/ALT ratio was established as a prognostic factor for cirrhosis (23, 24) and is highly correlated with Child-Pugh grade (21, 24). But our study showed that a high AST level still had a significantly independently predictive role in HCC survival after adjusting for the Child-Pugh grade of cirrhosis. It has been suggested that sinusoidal liver cells have a role in the clearance of AST activity from the serum (25). Therefore, it is possible that impaired sinusoidal function among patients with progressive fibrosis and cirrhosis results in a relative increase in the serum AST level. ALT is localized solely in the cellular cytoplasm, whereas AST is both cytosolic and mitochondrial. Progressive damage to mitochondrial structures has been considered to be responsible for the increase in the AST: ALT ratio as liver

Table V. *Clinical weights of predictors for sickness score to classify patients with small hepatocellular carcinoma (HCC) treated by percutaneous ethanol injection (PEI) and PEI plus transcatheter arterial chemoembolization (TACE) into high-, intermediate-, and low-risk group by tertile of sickness score, and three illustrative cases by risk group.*

Predictor	Risk Score			
	Clinical weight	Low (0-30)	Intermediate (31-50)	High (51-100)
Baseline	27			
Gender		Male	Male	Male
Male	22	•	•	•
Female	0			
Age at diagnosis, years		46	64	68
<55	8	•		
55-64	9		•	
≥65				•
Liver dysfunction		A	B	B
Child-Pugh A	0	•		
Child-Pugh B	25		•	•
Multiple tumour		Solitary	Solitary	Multiple
Solitary	0	•	•	
Multiple	19			•
Level of AST		34	50	102
≤56 IU/l	0	•	•	
>56 IU/l	24			•
Treatment modality		PEI only	PEI only	PEI only
PEI only	17	•	•	•
PEI+TACE	0			
Sickness score		24	48	99
Risk of HCC death				
1-Year		5.8%	10.9%	37.9%
5-Year		52.8%	76.6%	99.7%
10-Year		75.3%	93.3%	99.99%

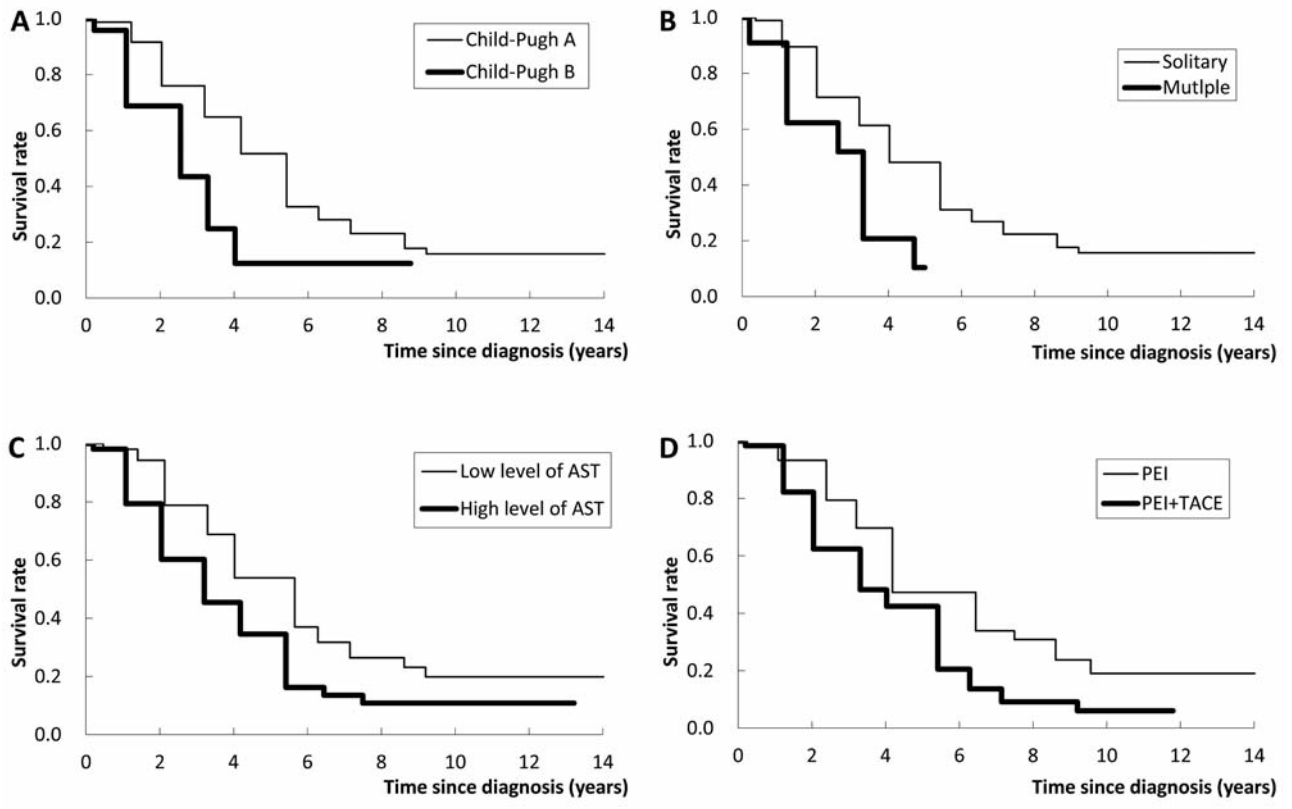

Figure 1. *Survival curve by Child-Pugh score (A), number of tumors (B), level of aspartate aminotransferase (AST) (C), and treatment modality (D). PEI: percutaneous ethanol injection; TACE: transcatheter arterial chemoembolization.*

disease worsens (22). A further larger study to elucidate the role of the AST level in the long-term survival of patients with HCC is needed. The AST level might also fluctuate during the follow-up period. The influence of long- term changes of AST level on survival for HCC should be further explored.

Our findings can be used to classify patients with small HCC treated with PEI and PEI combined with TACE into three groups, high-, intermediate-, and low-risk groups. Different clinical surveillance programs can, thus, be employed. Sonography or dynamic enhanced CT can be appropriately scheduled at shorter intervals (1-2 months) in the initial post-treatment period and adjuvant therapy (*e.g.* intensive focused radiotherapy) can also be considered for those in the high-risk group to achieve a better tumor control rate. From the description on the nine patients remaining alive, long-term survival among young patients is still possible if they have a small tumor and an early stage of liver cirrhosis, although they receive PEI treatment alone without surgical intervention.

It could be argued that the 12 deaths from liver cirrhosis could also be related to HCC. We have repeated the survival analysis by treating deaths due to HCC and liver cirrhosis together as the outcome of interest, and found one more statistically significant predictor, namely the cause of cirrhosis, after adjusting for age and gender. Alcohol-related HCC was responsible for a 2.72-fold (95% CI=1.41-5.27) increase in the risk of dying from either cause compared with hepatitis-related HCC. Child-Pugh score, level of AST, type of tumor and treatment modalities remained significant. When a multivariable model was repeated with adjustment for each variable, Child-Pugh score and level of AST remained statistically significant.

One limitation of this study is that the use of PEI for HCCs up to 5 cm is no longer the standard-of-care as new treatment modalities, such as microwave and radiofrequency ablation, have been proposed (26). In spite of these new treatment modes, our long-term results of the predictors after PEI provide good insight for countries that may not be able to yet implement these new treatment modalities.

In conclusion, our study found that Child-Pugh score of liver cirrhosis and AST level play an important role in the long-term survival of patients with small HCCs unsuitable for surgical treatment, making allowance for treatment modality. We also provide the predicted survival curves according to the combination of these clinical predictors, which are easily obtained in clinical daily practice. Our

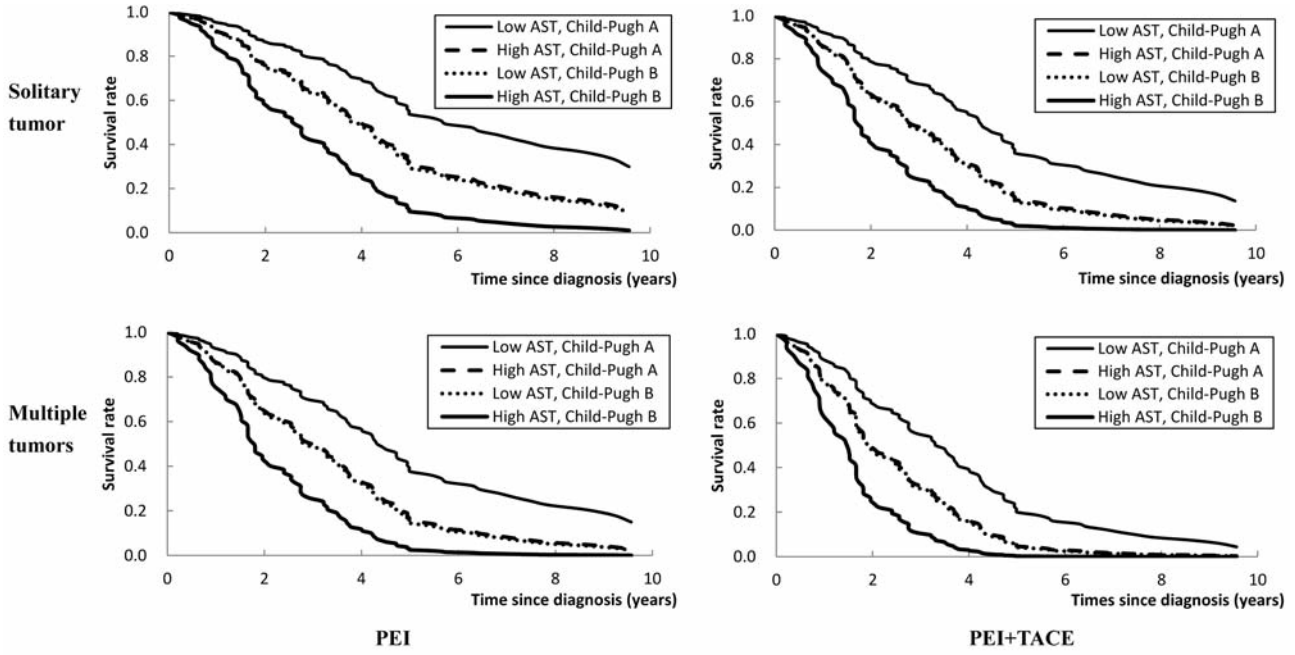

Figure 2. *Long-term survival rate of patients with hepatocellular carcinoma by treatment modality, number of tumors, level of aspartate aminotransferase (AST), and Child-Pugh score.*

findings could be very helpful for the classification of a high-risk group of patients with small HCCs treated by PEI alone or combined with TACE, and may contribute to developing different strategies of clinical surveillance for such patients.

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Received September 2, 2013
Revised October 17, 2013
Accepted October 18, 2013