RESEARCH ARTICLE

Prognostic Significance of Preoperative Serum Alpha-fetoprotein in Hepatocellular Carcinoma and Correlation with Clinicopathological Factors: a Single-center Experience from China

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Abstract

Objectives: To investigate the prognosis significance of preoperative serum alpha-fetoprotein (AFP) and the correlation with clinicopathological factors of hepatocellular carcinoma (HCC) patients who underwent hepatectomy. Materials and Methods: Clinicopathological data of retrospective analysis were collected for 251 HCC patients undergoing hepatectomy in this study. According to preoperative AFP level, patients were categorized into AFP-negative (0-20ng/mL) and AFP-positive (>20 ng/mL) groups for Kaplan-Meier analysis and Cox proportional hazard regression modeling. Results: The results demonstrated that increased AFP was associated with longer prothrombin time (PTs), liver capsule invasion, low grade differentiation, and late Barcelona Clinic Liver Center (BCLC) stage. Moreover, the female patients had a greater prevalence of increased preoperative AFP than male patients [284.8 (3.975-3167.5) *vs* (3.653-140.65); Z-2.895, *p*=0.004]. The 1-, 3-, and 5-year recurrence-free survival (RFS) rates were 78.1, 57.5, and 40.6 % in the AFP-negative group and 61.8, 37.7, and 31.4 %, respectively, in the AFP-positive group (log-rank test 8.312, *p*=0.004). The 1-, 3-, and 5-year overall survival (OS) rates were 94.4, 83.8, and 62.3% in the AFP-negative group and 87.2, 60.0, and 36.7%, respectively, in the AFP-positive group. The difference was statistically significant (log-rank test, 16.884, *p*=0.000). Cox proportional-hazards model identified preoperative AFP to be an independent prognostic predictor of overall survival. Conclusions: Preoperative serum AFP is an independent predictor of prognosis among HCC patients following surgical resection. Female patients have a higher preoperative AFP than their male counterparts.

Keywords: Hepatocellular carcinoma - alpha-fetoprotein - hepatectomy - survival

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and the third most frequent cause of cancer-related death. Half of these cases and deaths are estimated to occur in China (Ferlay et al., 2010; Jemal et al., 2011). Although there is substantial geographical variation, the greatest burden of the disease is in East Asia, Eastern Europe and sub-Saharan Africa, where hepatitis B virus (HBV) infection is highly prevalent (Yuen et al., 2009). HBV infection is the predominant cause of HCC development, associated with approximately half of all cases of HCC, and almost all cases of HCC in children (El-Serag et al., 2011). By contrast, in North America, Europe, and Japan, infection with hepatitis C virus (HCV) is the main risk factor. In addition to HBV and HCV infections, increasing age, male sex and chronic alcohol consumption are significant risk factors for the development of HCC. HCC incidence rates are increasing in many parts of the world including the United States and Central Europe, possibly due to these factors (Bosetti et al., 2008; Center et al., 2011).

Alpha-fetoprotein (AFP), a fetal specific glycoprotein, is synthesized in the liver of human embryos as early as 1 month after conception and is present in greatest quantities around the 3rd month of gestation, and its synthesis will cease at or near birth, and then the concentration will decline to a low level (Tomasi et al., 1977). In healthy adults, serum AFP concentration is below 20ng/ml. AFP has served as a useful biomarker for diagnosis of HCC since the 1970s, when most patients with HCC were diagnosed at an advanced stage and had clinical symptoms (Debruyne et al., 2008). Currently, liver ultrasonography (US) combined with AFP measurement every 6 months is the standard method of HCC surveillance in many Countries and regions (Kim et al., 2012).

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The prognosis value of AFP has been proposed in recent studies, although the clinical utility of AFP for HCC remains controversial. Some studies found that elevated serum AFP levels are a robust predictor of poor overall survival and recurrence-free survival (Chan et al., 2009; Lee et al., 2012). While, other researchers found that serum AFP is not a good prognostic indicator in small HCC, especially in HCC ≤2cm (Forner et al., 2008; Giannini et al., 2012).

Therefore, in this study, we collected and analyzed the clinical and follow-up information of HCC underwent hepatectomy to evaluate the prognostic role of AFP in Chinese patients. Moreover, we expect to reveal the differences of clinicopathological factors between the AFP-negative patients and the AFP-positive ones.

Materials and Methods

Patients

Between January 2006 and December 2011, two hundreds and fifty-one consecutive HCC patients (27 to 79 years of age) who underwent hepatectomy at the Cancer Institute and Hospital of Chinese Academy of Medical Science were enrollment in the study. The diagnostic criteria for HCC used in the study were in accordance with the American Association for the Study of Liver Diseases' 2005 guidelines. All patients had preoperative serum AFP levels >200ng/ml or a typical enhancement pattern (arterial enhancement and portal/delayed washed out) on dynamic imaging of hepatic mass (es) >2cm, or cytologic/histologic evidence of HCC

Preoperative procedures consisted of blood routine, liver and renal function, coagulation studies, screening for HBV/HCV markers, and determination of serum AFP, carcinoembryonic antigen (CEA), and carbohydrate antigen 199 (CA199)levels. Abdominal computed tomography scan with contrast or magnetic resonance imaging was routinely undertaken. Child-Pugh criteria were used for liver function evaluation. Tumor staging was evaluated according to the Barcelona Clinic Liver Cancer (BCLC) staging classification. All patients provided written informed consent before surgery and the treatments were performed in accordance with present ethical principles.

Sample classification

As the cut-off value for AFP is set at 20ng/ml in most studies (Debruyne Gupta et al., 2003; Zhang et al., 2010), the 251 cases were classified into two groups using this cut-off value; therefore, 142 cases were classified in the AFP-negative group (AFP≤20ng/ml), and 109 cases were classified in the AFP-positive group (AFP>20ng/ml).

Follow-up

All postoperative patients were followed at 3-monthly intervals for the first year and at 4- to 6-monthly intervals thereafter. The follow-up program included serum AFP assays, liver function tests, abdominal ultrasonography, and chest X-rays. Enhanced computed tomography or magnetic resonance imaging was performed every 6 months for surveillance of recurrence. Bone scanning was undertaken when necessary. In cases where a suspicious recurrent or metastatic lesion was detected, magnetic resonance imaging or hepatic angiography was employed to consolidate the diagnosis. The diagnosis of tumor recurrence was based on typical imaging features, an increase in serum AFP levels or development of extrahepatic metastasis. Fine needle aspiration/biopsies were not necessarily undertaken to assess recurrences.

Statistical analysis

Statistical analysis performed using SPSS version 17.0 software. Continuous variables of normal distribution were expressed as mean and SD and compared with the independent T-test. Continuous variables of non-normal distribution were expressed as medians and IQRs and compared with the Mann–Whitney U test. Categorical variables were compared by the chi-square test or Fisher's exact test as appropriate. Overall survival (OS) and recurrence-free survival (RFS) rates were evaluated by Kaplan-Meier survival estimates test, and the P values were assessed using log-rank tests. For multivariate analysis, the stepwise Cox's proportional-hazards models were used. In all cases, statistical significance was defined as $p<0.05$.

Results

Patient characteristics

The demographic, clinical, and pathologic characteristics of the 251 patients are shown in Table 1. There were 214 men and 37 women, with a mean age of 55 years (range 27-79). A total of 90.84% (228/251) of patients had hepatitis B or C virus infection and 86.45% (217/251) had liver cirrhosis of varying severity.

Comparison of the AFP-negative and AFP-positive groups

In our study, AFP displayed a sensitivity of 52.2%; the characteristics of the two groups are shown in Table 1. The AFP-positive group exhibited characteristics of poor tumor biological behavior (liver capsule invasion, and low grade differentiation), poor liver function (abnormal prothrombin time), and late BCLC stage.

Moreover, the female ratio in the AFP-positive group was higher than that in the AFP-negative group, and the difference was significant (24/109 *vs* 13/124, $p=0.004$). And, the female patients had a greater prevalence of increased serum preoperative AFP than male patients [284.8 (3.975-3167.5) *vs* (3.653-140.65); Z=-2.895, $p=0.004$].

Operative variables and perioperative outcomes

Operative and perioperative variables are summarized in Table 2. Total intra-operative blood loss and blood transfusion rates in the AFP-positive group were greater than in the AFP-negative group. In 72 patients with an uncomplicated procedure, hepatectomy was performed without blood occlusion. A selective and dynamic region-specific vascular occlusion (SDRVO) technique (Yu et al., 2014) was used in 153 patients. Pringle was performed during the operation in 26 patients. On postoperative day 3, the level of PTs in the AFP-positive group was

Table 1. Clinical and Pathologic Characteristics

Variables	AFP-negative group (n=142)	AFP-positive group (n=109)	*P* value
Age(years)	55.23±11.375	53.16±10.112	0.129
Sex			0.004
male	129	85	
female	13	24	
Cirrhotic liver (yes/no)	120/22	Dec-97	0.304
Chronic hepatitis			0.091
No	18	5	
HBV	113	97	
HCV	9	4	
HBV+HCV	2	3	
Alcohol intake (yes/no)	83/59	75/34	0.092
ALT (U/L)	34.00 (24.75-55.00)	32.00 (21.00-49.00)	0.079
GGT (U/L)	52.00 (30.75-79.25)	53.00 (32.00-91.00)	0.432
TBIL (umol/L)	11.30 (8.45-15.80)	12.45(8.98-16.15)	0.358
ALB (g/L)	41.18±4.013	40.95±4.538	0.678
PLT	150.58±48.948	146.78±52.848	0.558
PTs	11.95 (11.48-12.50)	12.15 (11.58-12.80)	0.038
BCLC staging			0.025
stage A	92	56	
stage B	45	43	
stage C	4	10	
Number of tumor			
1	126	96	0.871
≥2	16	13	
Tumor diameter(cm)mean ± SD	4.87±2.778	5.54±3.494	0.091
Blood vessel invasion (yes/no)	11/131	14/95	0.181
Liver capsule invasion (yes/no)	80/62	77/32	0.02
Differentiation			0
Well	26	2	
Moderate	93	70	
Poor	23	37	
incision margin			0.554
≤1.0cm	65	54	
>1.0cm	77	55	
Preoperative TACE (yes/no)	129/13	93/16	0.175

*Continuous variables of normal distribution were expressed as mean and SD and compared with the independent T-test. Continuous variables of non-normal distribution were expressed as medians and IQRs and compared with the Mann–Whitney U test. Categorical variables were compared by the chi-square test or Fisher's exact test as appropriate; BCLC Barcelona Clinic Liver Cancer, HBV hepatitis B virus, HCV hepatitisC virus, IQR interquartile SD standard deviation, TACE transarterial chemoembolization

significantly higher than in the AFP-negative group, but there was no significant difference between the two groups on postoperative day 7. Transient liver impairment was defined as Child's C status on postoperative day 7. The number of cases with post-operative massive hemorrhage, bile leakage, transient liver impairment, and 30-day operative mortality was 1, 5, 13, and 0, respectively, with no significant difference between the two groups.

Recurrence

HCC recurrence ratio in the AFP-positive group was higher than that in the AFP-negative group [69/109 (63.30%) *vs* 67/142 (47.18%); p=0.011]. Most recurrence (116/136) developed in liver and there were no differences between the two groups for the site or number of recurrence (Table 3). Most recurrence (110/136) occurred in 2 years after hepatectomy and the ratio in the AFP-positive group was higher than that in the AFP-negative group [61/69(88.41%) *vs* 49/67 (73.13%); p=0.024]. TACE was received by 70 patients as the main initial therapy for HCC recurrence. A total of 32 patients received potentially curative treatment for recurrence of HCC, including RFA in 24 patients and surgery in 8 patients.

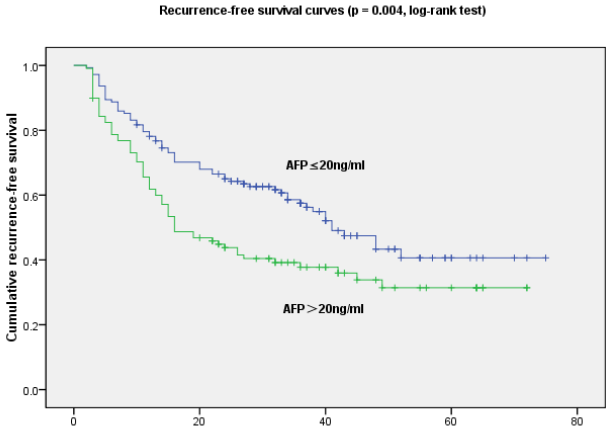

Figure 1. Recurrence-free Survival Time (Months)

The 1-, 3-, and 5-year recurrence-free survival rates for all patients were 77.1, 49.0, and 36.8 %, respectively. The rates were 78.1, 57.5, and 40.6% in the AFP-negative group and 61.8, 37.7, and 31.4%, respectively, in the AFP-positive group (Figure 1). The differences were statistically significant in favor of the AFP-negative group (log-rank test 8.312, p=0.004).

Table 2. Operative Variables and Peri-operative Outcomes

Variables	AFP-negative group (n=142)	AFP-positive group (n=109)	P value
Intraoperative variables			
Operative time (min)	195 (155-240)	210 (162.5-297.5)	0.072
Vascular occlusion			0.639
no	38	34	
SDRVO[a]	90	63	
Pringle	14	12	
Warm ischemia time (min)[b]	18 (10-15)	17 (0-25)	0.354
Total blood loss (ml)	300 (200-600)	500 (300-1200)	0.005
Blood transfusion (yes/no)	17/125	34/75	0
Postoperative outcome	2	3	
Alanine aminotransferase (U/L) 3 days	201.50 (129.75-298.25)	241.00 (121.00-429.00)	0.108
γglutamyltranspeptidase (U/L) 3 days	45.00 (25.75-76.00)	41.00 (30.25-64.00)	0.722
Total bilirubin (mmol/L) 3 days	18.90 (14.38-25.83)	18.80 (13.53-26.63)	0.936
Serum albumin (g/L) 3 days	28.03 (30.80-32.55)	27.65 (30.50-33.88)	0.781
PTs 3 days	12.45 (12.18-13.50)	12.56 (12.19-13.80)	0.041
Alanine aminotransferase (U/L) 7 days	67.50 (47.00-98.50)	90.00 (59.00-134.50)	0.168
γglutamyltranspeptidase (U/L) 7 days	85.00 (44.5-164.25)	76.50 (61.50-128.50)	0.957
Total bilirubin (mmol/L) 7 days	16.4 (11.33-21.15)	18.35 (10.88-30.55)	0.41
Serum albumin (g/L) 7 days	32.0 (30.03-34.25)	32.55 (30.58-35.90)	0.246
PTs 7 days	12.16 (11.56-12.93)	12.17 (11.59-12.96)	0.062
Massive hemorrhage	0	1	1
Bile leakage	3	2	1
Transient liver impairment[c]	7	6	0.839
30-day operative mortality	0	0	1
Postoperative hospital stay (day)	9 (7-12)	9 (7-13)	0.77

*Continuous variables of normal distribution were expressed as mean and SD and compared with the independent T-test. Continuous variables of non-normal distribution were expressed as medians and IQRs and compared with the Mann–Whitney U test. Categorical variables were compared by the chi-square test or Fisher's exact test as appropriate; [a]selective and dynamic region-specific vascular occlusion; [b]Total ischemia time for selective and dynamic region-specific vascular occlusion; [c]Child's C status on postoperative day 7

Table 3. Characteristics and Treatment of Recurrent HCC

Variables	AFP-negative group (n=142)	AFP-positive group (n=109)	P value
Number of recurrence	67	69	0.011
site of recurrence			0.943
IHR	57	59	
EHR	10	10	
recurrence time			0.024
in 2 years	49	61	
>2 years	18	8	
treatment for recurrence[a]			0.892
TACE	35	35	
RFA	11	13	
Surgery	5	3	
Radiotherapy	0	1	
Sorafenib	2	2	
Supportive treatment	14	15	

*EHR extrahepatic recurrence, HCC hepatocellular carcinoma, IHR intrahepatic recurrence, RFA radiofrequency ablation, TACE transarterial chemoembolization; Variables were compared by the chi-square test or Fisher exact test as appropriate. The first recurrences that were recorded; [a]The initial treatment for first recurrence

Survival

The median follow-up was 44(3-75) months. There were 85 (33.86 %) deaths at the time of data censor. In the AFP-negative group, 33 patients died as a result of tumor progression, in the AFP-positive group, the causes of death were tumor progression (52 patients) and liver failure (one patient). The 1-, 3-, and 5-year overall survival rates for all patients were 91.2, 73.5, and 50.9% respectively. The rates were 94.4, 83.8, and 62.3% in the AFP-negative group and 87.2, 60.0, and 36.7%, respectively, in the AFP-positive group (Figure 2). The difference was statistically significant (log-rank test 16.884, p=0.000).

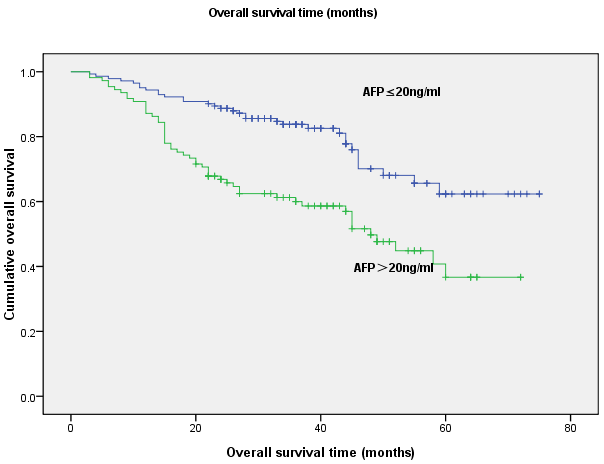

Figure 2. Overrall Survival Time (Months)

Prognostic factors

We performed an analysis of prognostic factors for recurrence and survival. Exploratory multivariate analysis using a stepwise Cox proportional-hazards model identified three characteristics as independent prognostic predictors of recurrence (Table 4). These were tumor diameter (HR 1.158; 95%CI 1.067-1.256; p=0.000), blood vessel invasion (HR 1.677; 95%CI 1.009-2.787;

Table 4. Univariate and Multivariate Analysis of Predictive Factors for Recurrence Free Survival

Variables	Univariate analysis		Multivariate analysis	
	HR(95.0%CI)	*p* value	HR(95.0%CI)	*p* value
Age	1.010(0.994-1.026)	0.225		
Sex	1.011(0.622-1.624)	0.965		
Chronic hepatitis	0.924(0.658-1.298)	0.648		
Alcohol intake	1.025(0.725-1.450)	0.888		
Cirrhotic liver	1.414(0.813-2.460)	0.22		
AFP	1.626(1.259-2.280)	0.005	1.325(0.921-1.907)	0.129
ALT	0.999(0.994-1.004)	0.763		
GGT	1.001(0.999-1.003)	0.321		
TBIL	1.004(0.995-1.014)	0.39		
ALB	0.972(0.933-1.012)	0.163		
PLT	0.999(0.996-1.003)	0.602		
PTs	1.077(0.884-1.312)	0.463		
Number of tumor	1.609(1.021-2.537)	0.04	1.393(0.858-2.261)	0.18
Tumor diameter	1.170(1.113-1.230)	0	1.158(1.067-1.256)	0
Liver capsule invasion	2.010(1.380-2.927)	0	1.318(0.874-1.988)	0.188
Blood vessel invasion	2.285(1.403-3.721)	0.001	1.677(1.009-2.787)	0.046
Differentiation	1.770(1.316-2.381)	0	1.487(1.075-2.059)	0.017
BCLC staging	1.775(1.356-2.325)	0	0.840(0.541-1.305)	0.438
incision margin	1.066(0.760-1.496)	0.712		
Operative time	1.001(0.999-1.003)	0.521		
Warm ischemia time	0.995(0.980-1.011)	0.552		
Blood transfusion	1.577(1.068-2.327)	0.022	1.090(0.696-1.707)	0.708
Preoperative TACE	1.478(0.887-2.463)	0.113		

Table 5. Univariate and Multivariate Analysis of Predictive Factors for Overall Survival

Variables	Univariate analysis		Multivariate analysis	
	HR(95.0%CI)	*p* value	HR(95.0%CI)	*p* value
Age	1.011 (0.992-1.031)	0.248		
Sex	1.091 (0.604-1.970)	0.773		
Chronic hepatitis	0.886 (0.583-1.349)	0.574		
Alcohol intake	0.791 (0.503-1.243)	0.309		
Cirrhotic liver	1.721 (0.794-3.731)	0.169		
AFP	2.417 (1.561-3.743)	0	1.767 (1.108-2.816)	0.017
ALT	0.995 (0.986-1.003)	0.233		
GGT	1.002 (0.999-1.004)	0.149		
TBIL	1.009 (1.000-1.018)	0.047	1.675 (0.903-3.106)	0.102
ALB	0.969 (0.919-1.021)	0.242		
PLT	0.997 (0.992-1.001)	0.171		
PTs	1.038 (0.808-1.333)	0.77		
Number of tumor	2.313 (1.408-3.800)	0.001	1.857 (1.071-3.221)	0.028
Tumor diameter	1.207 (1.145-1.272)	0	1.135 (1.105-1.245)	0.007
Liver capsule invasion	2.371 (1.436-3.918)	0.001	1.242 (0.701-2.241)	0.458
Blood vessel invasion	2.171 (1.200-3.927)	0.01	1.606 (0.859-3.005)	0.138
Differentiation	2.234 (1.535-3.253)	0	1.701 (1.116-2.594)	0.014
BCLC staging	2.598 (1.872-3.605)	0	1.224 (0.720-2.081)	0.454
incision margin	0.957 (0.625-1.466)	0.841		
Operative time	1.002 (1.000-1.005)	0.048	1.000 (0.998-1.003)	0.762
Warm ischemia time	0.994 (0.974-1.015)	0.592		
Blood transfusion	1.672 (1.043-2.683)	0.033	0.945 (0.515-1.735)	0.855
Preoperative TACE	2.143 (1.202-3.822)	0.01	1.589 (0.832-3.035)	0.16

p=0.046), and tumor differentiation (HR 1.487; 95%CI 1.075-2.059; *p*=0.027).

Exploratory multivariate analysis using a stepwise Cox proportional-hazards model identified three variables as independent prognostic risk factors for survival (Table 5). These were preoperative AFP level (HR 1.767; 95%CI 1.108-2.816; *p*=0.017), number of tumor (HR 1.857; 95%CI 1.071-3.221; *p*=0.028), tumor diameter (HR 1.135; 95%CI 1.105-1.245; *p*=0.007), and tumor differentiation (HR 1.701; 95%CI 1.116-2.594; *p*=0.014).

Discussion

This study shows that preoperative serum AFP level is predictive of mortality after surgical resection independently of other prognostic factors. Although high

AFP level increased risk of recurrence, it was not an independent negative prognosis factor for recurrence free survival by multivariate analysis. Increased preoperative serum AFP level has been reported by a large number of other studies to be an adverse prognostic factor both in early and advanced stages of HCC (Savastano et al., 1999; Ikai et al., 2004; Peng et al., 2004; Sugita et al., 2008). The finding of this study that AFP is independently predictive of poor survival is consistent with results of these studies.

In this study, we found that preoperative AFP levels in the female were higher than that in male patients. This finding was similar to some researchers (Zhou et al., 2013; Li et al., 2014). However, it is not unknown that the mechanism and clinical value of this finding.

Despite these promising results, the clinical use of AFP has been also shown to present some important limitations in sensitivity and specificity. In fact, low AFP levels have been described in HCC patients, while high levels might be detected in hepatic cirrhosis without HCC (Bertino et al., 2011). For instance, the level of AFP was increased in only 38% patients developing small HCC nodules (Sangiovanni et al., 2004). Indeed, AFP might be also useful in detecting other tumors (such as germ cell tumors of the ovary and testis and colorectal cancer) (Haibin et al., 2010; Nakagawa et al., 2012). The study by Giannini et al failed to show a prognostic value of AFP in well-compensated cirrhotic patients with single, small HCC (<3cm) treated with curative intent (Giannini et al., 2012). And, it's reported that AFP levels had no prognostic usefulness for female patients, probably because female patients usually had normal liver function, a lesser proportion of cirrhosis, and a greater proportion of single and small tumors, which may weaken the prognostic value of AFP (Li et al., 2014). Higher AFP level has been found to be associated with poorly differentiated tumors, biliary involvement, multifocal HCC, portal vein thrombosis, which themselves are known to be adverse prognostic factors in HCC (Nomura et al., 1989; Zhou et al., 2013). And it indicates that the prognosis value of preoperative AFP is affected by these factors to some extent. In our study, increased AFP exhibited characteristics of liver capsule invasion, low grade differentiation, and late BCLC stage. Thus, although currently recommended as a fundamental parameter for HCC screening in patients with cirrhosis, the prognostic capability of AFP in patients with HCC remains controversial and with important limitations. Our study shows that preoperative serum AFP is an independent adverse prognostic factor for mortality after surgical resection, independently of other prognostic factors including tumor size, tumor number, tumor grade differentiation, biliary or vascular involvement, and BCLC stage.

So far, it was not unclear that the exact mechanism of how AFP could be a prognostic indicator for HCC. Most researchers believe that AFP is released as a result of hepatocarcinogenesis, and is hence reflective of the proliferative activity and tumor burden. AFP may promote the proliferation of NIH 3T3 cells by binding its receptor to trigger the signal transduction pathway of cAMP-PKA and alter the expression of K- ras p21 gene (Li et al., 2002). AFP showed a capability to promote HepG2 cells by 3.5 folds, and the percentage of HepG2 cells in S phase was modestly increased after exposure to AFP (Li et al., 2011). AFP may play a regulatory role on angiogenesis and cell invasion during HCC development by increasing expression of vascular endothelial growth factor, vascular endothelial growth factor receptor 2, matrix metalloproteinases-2/9 (Meng et al., 2014). AFP may positively regulate cell proliferation by enhancing the apoptosis resistance via dysfunction of the p53/Bax/cytochrome c/caspase-3 signaling pathway in AFP-producing HCC cell line (Yang et al., 2008). These findings suggest that AFP elevation might not only be just an epiphenomenon of malignant transformation, but may also actively participate in tumor proliferation.

The expression of AFP is regulated by many factors in different stages. Transcriptionally, AFP expression is regulated by a promoter region, a repressor region, and 3 enhancer regions. The promoter region is responsible for initiating AFP expression and binding of several transcription factors including hepatocyte nuclear factor-3 alpha (HNF-3alpha), hepatocyte nuclear factor-1 (HNF-1), nuclear factor 1 (NF-1), and CAAT/enhancer binding protein (C/EBP) (Bois-Joyeux et al., 1994; Crowe et al., 1999). The repressor activity is modulated by binding of several transcription repressors such as zinc finger protein ZBTB20 and p53 represses AFP transcription. During carcinogenesis, various signaling pathways such as microRNA122/CUX1 deregulation and p53 mutation modulate the activity of these repressors, thereby alleviating AFP repression and AFP expression increasing (Kojima et al., 2011). Moreover, HBV viral protein, HBx, disrupts p53-mediated AFP repression through an association with DNA-bound p53, and large numbers of HBV integration into the host genome correlate with high serum AFP levels (Ogden et al., 2000; Sung et al., 2012). However, the detailed mechanisms of the AFP expression are still not completely understood.

In summary, preoperative serum AFP is a predictor of overall survival and recurrence-free survival independent of other clinicopathological factors among patients following surgical resection. The female patients had a higher preoperative AFP than male patients.

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