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Liver

Postoperative α-fetoprotein response predicts tumor recurrence and survival after hepatectomy for hepatocellular carcinoma: A propensity score matching analysis

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ABSTRACT

Background: To investigate the prognostic values of the change of α-fetoprotein within 1 week after resection of hepatocellular carcinoma.

Methods: We retrospectively analyzed patients with hepatocellular carcinoma who underwent curative hepatectomy as primary therapy at Zhongshan Hospital, Fudan University (Shanghai, China) from 2009 to 2011. We measured serum α-fetoprotein before (α-fetoprotein$_0$) and 1 week after (α-fetoprotein$_7$) hepatectomy, calculated change of α-fetoprotein, namely the α-fetoprotein response by the formula: AR = lgAFP$_7$/lgAFP$_0$ (lg = log$_{10}$), analyzed the relationship between patient survival and α-fetoprotein response, and explored the potential clinical implications of the α-fetoprotein response. The results were validated in an independent cohort of patients from the same institute.

Results: A total of 841 eligible patients were analyzed. We determined that the optimal cutoff value of the α-fetoprotein response was 0.8135 and subsequently classified patients from the exploration cohort into the α-fetoprotein responder (α-fetoprotein response $\leq$ 0.8135; $n = 452$) and α-fetoprotein nonresponder (α-fetoprotein response > 0.8135; $n = 146$). Multivariate Cox analysis showed that the α-fetoprotein response independently predicted overall survival (OS) and recurrence-free survival (RFS) time after resection (both $P < .001$). In patients with a higher risk of tumor recurrence (either single tumor with microvascular invasion or multiple tumors), α-fetoprotein responders were associated with better survival than the nonresponders ($P < .05$). The results were validated by propensity score matched population and another independent cohort.

Conclusion: The α-fetoprotein response is a reliable and simple predictive marker for evaluating the oncological effect of surgical resection for hepatocellular carcinoma with positive α-fetoprotein before resection, independent of tumor features.

Introduction

Liver cancer, primarily hepatocellular carcinoma (HCC), is the fifth most common cancer and the second most common cause of cancer-related mortality in the world.[1] Surgical resection and local ablation are currently the best treatment options for early-stage HCC. In some centers, the indication for resection extends to the Barcelona Clinic Liver Cancer (BCLC) intermediate stage.[2–5] However, the 5-year recurrence rate of HCC after surgery was reported to be more than 60%–80%, which significantly undermines long-term survival.[6–8]

The incidence of tumor recurrence within 2 years (ie, early recurrence) after resection is around 50%.[9,10] It is recognized that early recurrence mainly originates from occult tumor lesions that were not identified before or during resection.[11,12] It is well accepted that the risk of early recurrence is associated with tumor factors, such as the presence of microvascular invasion (MVI), tumor numbers, and tumor size. Liver-related factors, such as the hepatitis B virus load,[13] the presence of hepatitis B virus e antigen (HBeAg),[14] or the hepatitis B virus c antibody (HBcAb),[15] also contribute to the risk of early recurrence. On the other hand, the extent and style of the resection may also affect the risk of the early recurrence. Anatomic resection or wide surgical margin provide

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better survival compared with nonanatomic resection in patients with multiple tumors or MVI.[16,17] Patient survival largely depends on the oncologic effect of liver resection for HCC, early evaluation of which will facilitate individualized follow-up strategies and adjuvant therapies aimed at decreasing or delaying tumor recurrence. The oncologic effect is usually evaluated by traditional imaging techniques after surgery, however, which are not sensitive enough to detect lesions of less than 2 cm.[18]

One of the most widely used tumor markers for HCC is α-fetoprotein (AFP).[19] The diagnostic value of AFP has been intensively studied and debated.[20–22] In patients with HCC, AFP level is associated with tumor burden,[23,24] and theoretically a change in AFP could be used to reflect a change in tumor burden. Indeed, several studies have reported that serial changes in the AFP level after therapies, such as systemic chemotherapy,[25,26] hepatic artery infusional chemotherapy,[27] concurrent chemoradiation therapy,[28] transarterial chemoembolization (TACE),[29,30] or combined radiotherapy[31] and radiofrequency ablation (RFA),[32] could be a marker for tumor response. A few studies have demonstrated that a loss of serum AFP after resection predicted time to recurrence and survival.[33,34] The half-life of AFP after resection of HCC has especially been used to link the decline of AFP with the oncologic effect of hepatectomy, providing a useful indicator to evaluate outcomes after resection.[35] However, it requires a preoperative AFP > 100 ng/mL, as well as a delay of 1 month after liver resection to calculate the AFP half-life.

We hypothesize that the change of AFP level in 1 week after resection (namely, the AFP response [AR]) could be used to evaluate the oncologic effect of hepatectomy for HCC. In the present study, we therefore measured serum AFP before and after resection and investigated the prognostic value of the AR.

Methods

Patients

This retrospective study examined data collected from consecutive cases of HCC in patients treated at Zhongshan Hospital, Fudan University (Shanghai, China), from January 1, 2009, to December 31, 2011 (the exploration cohort), and from January 1, 2012, to December 31, 2012 (the validation cohort). The inclusion criteria for the study population were as follows: (1) stage 0 to B according to the Barcelona Clinic Liver Cancer (BCLC) classification; (2) class A liver function according to the Child-Pugh classification; (3) surgical resection as the initial treatment for HCC, defined as a local radical procedure (R0) with tumor-negative resection margins; (4) HCC confirmed by postoperative pathologic examination; and (5) preoperative serum AFP value exceeding 20 ng/mL (upper limit of the normal value) and below 60500 ng/mL (maximum measuring range of the assay [Roche Diagnostics, Indianapolis, IN] used to detect AFP in our hospital) and checked at 1 week and 1 month after resection. The exclusion criteria included the following: (1) presence of other malignancies, (2) previous antitumor treatment, (3) incomplete data, and (4) loss to follow-up (Fig 1). This study was approved by the Hospital Research Ethics Committee. Informed consent was obtained from the patients.

Clinicopathologic factors known to be related to tumor recurrence and survival were selected on the basis of earlier studies,[36,37] including age (cutoff values were the mean ages of patients), sex (male or female), hepatitis B antigens (HBsAg and HBeAg, positive or negative), tumor size (≤5 cm or >5 cm), the number of tumor nodules (1 or > 1), MVI (absent or present), and serum AFP concentration before resection. The preoperative laboratory tests included the serum alanine aminotransferase concentration ([ALT] ≤ 40 or > 40 U/L), albumin concentration ([ALB] ≤ 35 or > 35 g/L), and γ-glutamyl transpeptidase concentration ([GGT] ≤ 45 or > 45 U/L).

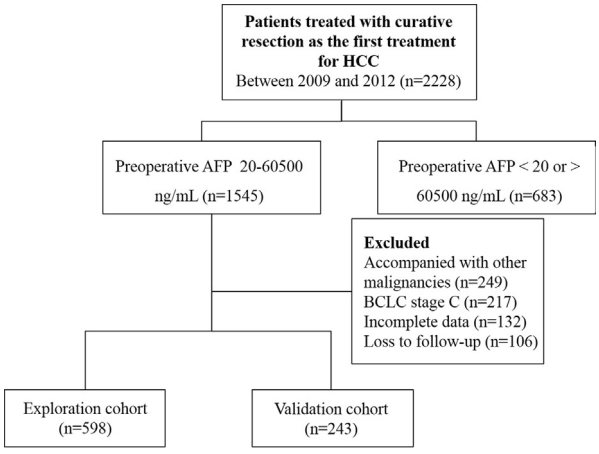

Fig 1. Flowchart of this study.

Follow-up and postoperative treatments

The patients were followed regularly, as described elsewhere, until January 2018.[14] Diagnosis of tumor recurrence was based on at least two imaging methods. Treatment modalities after tumor recurrence were administered according to a uniform guideline.[14] Overall survival (OS) was calculated from the date of surgery to the date of death, or censored on the last follow-up. Recurrence-free survival (RFS) was defined as the interval between the date of surgery and tumor recurrence (intrahepatic recurrence and/or metastasis) or death. A high risk of tumor recurrence was defined as a single tumor with microvascular invasion or multiple tumor nodules.[38,39]

AFP response

The AR was calculated using the following formula:

$$AR = lgAFP_7/lgAFP_0$$

where AFP_0 was the baseline AFP concentration (preoperative serum AFP concentration within 3 days before resection), AFP_7 was obtained from an average value on day 6 to 8 after surgery, and lg refers to log_{10}. Because the distribution of AFP values was skewed and their range was very wide (20.3–59,900.0 ng/mL), the values were transformed into logarithmic form and the Gaussian distribution of AR was obtained (Supplementary Fig 1).

In theory, a residual tumor may result from an intrahepatic metastasis or an occult multicentric tumor. It is generally accepted that recurrence from intrahepatic metastasis will take place within a short time after resection, but recurrence with a multicentric origin will take longer to develop a new lesion.[40] We use very-early recurrence (VER)—within 6 months after resection—as the indicator for incomplete removal, a timeframe making it less likely to be a multicentric new lesion. The optimal cutoff value of AR was determined using the receiver operating characteristic (ROC) curve for patients with and without very-early recurrence.

Statistical analysis

Propensity score matching (PSM) was developed in an attempt to reduce bias from different distribution of variables in the

Table I
Baseline characteristics of the two groups in the exploration cohort before and after PSM

Variables	Before PSM			After PSM		
	AFP responder $n = 452$	AFP nonresponder $n = 146$	*P* value	AFP responder $n = 163$	AFP nonresponder $n = 98$	*P* value
Age, years*	52.8 ± 10.9	50.7 ± 11.6	.054	53.1 ± 11.6	50.5 ± 12.0	.080
Sex			.143			.060
Male	366 (81%)	126 (86%)		120 (74%)	82 (88%)	
Female	86 (19%)	20 (14%)		43 (26%)	16 (16%)	
Baseline laboratory test result						
TB, μmol/L†	12.0 (9.0, 14.6)	11.3 (9.0, 14.5)	.707	11.1 (8.1, 14.3)	11.3 (9.1, 14.4)	.379
ALT, U/L†	33.3 (23.2, 44.9)	35.1 (22.9, 47.8)	.508	32.7 (22.0, 44.9)	32.1 (22.8, 42.2)	.902
ALB, g/L*	40.8 ± 3.3	39.7 ± 2.9	< .001	40.3 ± 3.1	40.0 ± 3.0	.426
GGT, U/L†	56.3 (34.6, 95.4)	59.2 (38.5, 103.0)	.332	65.8 (35.0, 107.2)	53.7 (35.9, 88.2)	.213
PT, s†	11.9 (11.3, 12.5)	12.0 (11.5, 12.6)	.216	12.1 (11.3, 12.5)	12.1 (11.5, 12.8)	.252
HBsAg			.252			.118
positive	396 (88%)	133 (91%)		139 (85%)	90 (92%)	
negative	56 (12%)	13 (9%)		24 (15%)	8 (8%)	
HBeAg			.246			.265
positive	123 (27%)	47 (32%)		49 (30%)	36 (37%)	
negative	329 (73%)	99 (68%)		114 (70%)	62 (63%)	
Preoperative lgAFP, ng/mL†	2.3 (1.8, 2.8)	3.5 (2.6, 4.1)	< .001	2.8 (2.2, 3.4)	3.0 (2.4, 3.6)	.139
No. of tumor			.317			.790
1	401 (89%)	125 (86%)		148 (91%)	88 (90%)	
> 1	51 (11%)	21 (14%)		15 (9%)	10 (10%)	
Tumor size, cm†	4.0 (2.5, 6.0)	5.0 (3.0, 8.1)	.001	4.0 (2.5, 6.5)	4.0 (2.5, 6.6)	.712
Tumor size, cm			< .001			.690
≤ 5	313 (69%)	79 (54%)		112 (69%)	65 (66%)	
> 5	139 (31%)	69 (46%)		51 (31%)	33 (34%)	
MVI			.290			.860
present	188 (42%)	68 (47%)		65 (40%)	38 (39%)	
absent	264 (58%)	78 (53%)		98 (60%)	60 (61%)	
BCLC stage			.187			.959
0	90 (20%)	20 (14%)		31 (19%)	19 (19%)	
A	311 (69%)	105 (72%)		117 (72%)	69 (71%)	
B	51 (11%)	21 (14%)		15 (9%)	10 (10%)	

PSM, propensity score matching; *AFP*, α-fetoprotein; *TB*, total bilirubin; *ALT*, alanine aminotransferase; *ALB*, albumin; *GGT*, γ-glutamyl transpeptidase; *PT*, prothrombin time; *HBsAg*, hepatitis B s antigen; *HBeAg*, hepatitis B e antigen; *MVI*, microvascular invasion.
* Student's *t* test.
† Mann–Whitney *U* test.

groups.[16,36] Variables that are statistically differently distributed in 2 groups were included in the generation of propensity scores from 0 to 1 for each patient. A 2:1 neighborhood match, using a caliper width of 0.1, without replacement between AFP responder and nonresponder was performed to generate patients into subsequent analysis.

Continuous variables were expressed as mean (± standard deviation) or median (interquartile range) as appropriate and compared using the Student's *t* test or the Mann–Whitney *U* test. Categorical variables were compared using the χ^2 test or the Fisher exact test. Survival curves were calculated using the Kaplan–Meier method and compared using the log-rank test. The multivariate Cox proportional hazards regression model was used to evaluate the independent prognostic factors of OS and RFS.

All statistical tests were two tailed, and a P value < .05 indicated a significant difference. Statistical analyses were performed using SPSS v 22.0 (IBM, Armonk, NY) and R v 3.4.0.

Results

Patients and AFP response

A total of 841 patients were included in the exploration cohort ($n = 598$) and the validation cohort ($n = 243$). The median follow-up duration was 55.5 months (range, 1.5–88.5 months). Overall, 511 patients (60.8%) had tumor recurrence and 333 patients (39.6%) died by the end of the last follow-up. AFP was measured on day 6 and day 8 but not on day 7 in 4.3% of patients (26 of 598) in the exploration cohort, and 4.9% (12/243) in the validation cohort. Therefore, for these patients, AFP on day 7 was estimated by the average value of AFP measured on day 6 and day 8.

For the patients in the exploration cohort, the median AR was 0.773 (range, 0.498–0.988). Supplementary Fig 2 presents that the area under the receiver operating characteristic curve (AUROC) for AR was 0.63 for the patients in the exploration cohort, and the optimal cutoff value was 0.8135 to predict early tumor recurrence. The patients in the exploration cohort were then divided into the AFP responder (AR ≤ 0.8135, $n = 452$) and AFP nonresponder (AR > 0.8135, $n = 146$).

The clinical characteristics for each group are described in Table I. Compared with AFP responders, AFP nonresponders tended to have a lower ALB, higher preoperative AFP, and larger tumor size. The PSM was conducted between AFP responder and nonresponder at a ratio of 2:1, using these three variables (ALB, preoperative AFP, and tumor size). The clinical and histologic variables had very similar distributions between the 2 groups after PSM (Table I).

Survival of patients and prognostic factors in the exploration cohort

Of the 598 patients in the exploration cohort, 364 had tumor recurrence and 241 died by the last follow-up. The 1-, 3-, and 5-year OS rates were 91.6%, 74.5%, and 65.0% in the AFP responders, respectively, which were higher than those of the AFP nonresponders (83.6%, 61.4%, and 45.7%, respectively, $P < .001$; Fig 2, *A*). The 1-, 3-, and 5-year RFS rates were 78.1%, 53.2%, and 44.3%, respectively, in the AFP responders and 58.2%, 38.3%, and 26.8%,

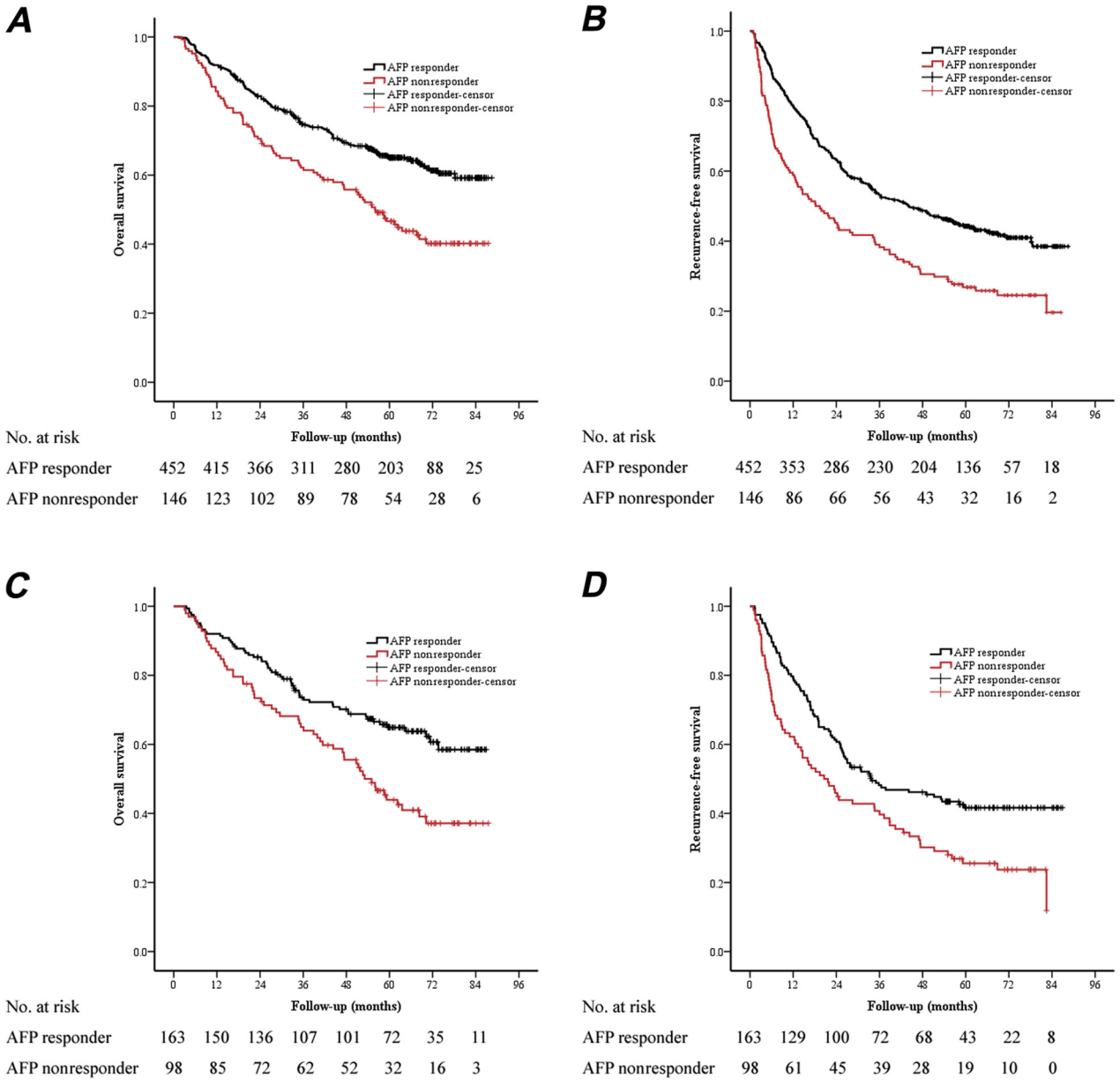

Fig 2. Kaplan–Meier curves for OS and RFS in HCC patients in the exploration cohort. (*A* and *B*) OS and RFS were significantly better in AFP responders than in AFP nonresponders in the whole population of the exploration cohort before PSM (both $P < .001$). (*C* and *D*) OS and RFS were significantly better in AFP responders than in AFP nonresponders in the exploration cohort after PSM (both $P < .001$).

respectively, in the AFP nonresponders ($P < .001$, Fig 2, *B*). A log-rank test followed by the multivariate Cox analysis identified 4 independent prognostic factors of both OS and RFS: AFP nonresponder, multiple tumors, the presence of MVI, and GGT > 45 U/L (Table II).

After the PSM, the variables between the 2 groups were not significantly different. We found AFP responders still yielded a better OS ($P < .001$, Figure 2C) and RFS ($P < .001$, Figure 2D) than AFP nonresponders, and AFP response was also an independent prognostic factor of both OS and RFS (Table II).

In the exploration cohort, 367 patients whose AFP dropped to a normal value within 1 month after hepatectomy were classified as early AFP complete resolution (early AFP CR) elsewhere.[35] Another 231 patients' AFP levels were still above 20 ng/mL 1 month after hepatectomy. Among the patients with early AFP CR, the OS ($P = .012$, Fig 3, *A*) and RFS ($P = .002$, Fig 3, *B*) of AFP responders were both better than AFP nonresponders. We observed no significant differences between AFP nonresponders with AFP CR at 1 month and patients with positive AFP at 1 month in both OS ($P = .844$, Fig 3, *A*) and RFS ($P = .726$, Fig 3, *B*). These results suggested that AR could be used to identify patients with a higher risk of tumor recurrence even in the patients with complete AFP resolution at 1 month. Despite AFP CR at 1 month, AFP nonresponders still had a survival rate as bad as those with positive AFP at 1 month.

As presented in Fig 3 (*C* and *D*), AFP responders had better OS and RFS than AFP nonresponders in HCC patients with a low risk or high risk of tumor recurrence (ie, a single tumor with MVI or multiple tumor nodules, all $P < .05$). AFP responders with a low risk of tumor recurrence had the best survival compared with other patient categories (all $P < .001$). The RFS of AFP nonresponders with a low risk of tumor recurrence was similar to that of patients with a high risk of tumor recurrence, with no distinction based on

Table II
Univariate and multivariate analysis of predictive factors for overall and recurrence-free survival in the exploration cohort before and after PSM

Variables	Overall survival				Recurrence-free survival			
	Univariate *P* value	Multivariate analysis			Univariate *P* value	Multivariate analysis		
		HR	95% CI	*P* value		HR	95% CI	*P* value
Before PSM								
Age (≤52/>52 years)	.379				.348			
Sex (female/male)	.143				.019	1.194	0.891–1.601	.235
ALT (≤40/>40 U/L)	.059				<.001	1.300	1.042–1.623	.020
GGT (≤45/>45 U/L)	< .001	1.536	1.143–2.064	.004	< .001	1.366	1.067–1.749	.013
ALB (>35/≤35 g/L)	.235				.076			
HBsAg (negative/positive)	.264				.011	1.455	0.988–2.115	.058
HBeAg (negative/positive)	.001	1.504	1.150–1.965	.003	.006	1.174	0.932–1.478	.173
MVI (absent/present)	< .001	1.670	1.294–2.155	< .001	< .001	1.396	1.133–1.720	.002
Tumor size (≤5/>5 cm)	< .001	1.022	0.733–1.425	.896	< .001	1.149	0.878–1.502	.312
Tumor number (1/> 1)	< .001	2.284	1.543–3.381	< .001	< .001	1.664	1.186–2.334	.003
Preoperative AFP (≤400/>400 ng/mL)	.020	1.201	0.914–1.579	.188	.001	1.048	0.839–1.308	.680
AFP responder/Nonresponder	< .001	1.577	1.186–2.098	.002	< 0.001	1.573	1.234–2.006	< .001
After PSM								
Age (≤52/>52 years)	.257				.226			
Sex (female/male)	.731				.223			
ALT (≤40/>40 U/L)	.538				.005	1.308	0.939–1.822	.112
GGT (≤45/>45 U/L)	.064				.002	1.423	0.988–2.048	.058
ALB (≤35/>35 g/L)	.951				.543			
HBsAg (negative/positive)	.068				.003	2.118	1.148–3.906	.016
HBeAg (negative/positive)	.018	1.565	1.077–2.275	.019	.015	1.186	0.844–1.665	.325
MVI (absent/present)	0.001	1.802	1.249–2.601	.002	.001	1.561	1.146–2.126	.005
Tumor size (≤5/>5 cm)	0.112				.040	1.247	0.833–1.867	.284
Tumor No. (1/> 1)	0.002	2.193	1.307–3.681	.003	.008	1.226	0.706–2.129	.470
Preoperative AFP (≤400/>400 ng/mL)	0.230				.977			
AFP responder/Nonresponder	.001	1.771	1.228–2.555	.002	.001	1.658	1.217–2.258	.001

PSM, propensity score matching; *AFP*, α-fetoprotein; *ALT*, alanine aminotransferase; *ALB*, albumin; *GGT*, γ-glutamyl transpeptidase; *HBsAg*, hepatitis B s antigen; *HBeAg*, hepatitis B e antigen; *MVI*, microvascular invasion; *HR*, hazard radio; *95%CI*, 95% confidence interval.

whether they were AFP responders ($P = .841$) or nonresponders ($P = .060$). The OS and RFS of the AFP responders with a high risk of tumor recurrence were worse than those of AFP responders with a low risk of tumor recurrence (both $P < .001$), but better than those of AFP nonresponders with a high risk of tumor recurrence (both $P < .05$).

In the patients with AFP7 ≤ 20 ng/mL ($n = 133$), AR is able to differentiate responders and nonresponders and predict RFS ($P = .003$, Supplementary Fig 3).

Validation

In the validation cohort, patients were divided into 2 groups by the cutoff value of 0.8135 as we discussed earlier in this report, the AFP responders (AR ≤ 0.8135, $n = 192$) and AFP nonresponders (AR > 0.8135, $n = 51$). The 1-, 3-, and 5-year OS rates were 90.1%, 76.9%, and 66.7% in the AFP responders, respectively, which were higher than those of the AFP nonresponders (70.6%, 50.8%, and 40.7%, respectively, $P < .001$; Supplementary Fig 4, *A*). The 1-, 3-, and 5-year RFS rates were 76.0%, 54.1%, and 43.6%, respectively, in the AFP responders and 52.9%, 29.0%, and 20.7%, respectively, in the AFP nonresponders ($P < .001$; Supplementary Fig 4, *B*). A log-rank test followed by multivariate Cox analysis identified the AFP response as an independent prognostic factor of both OS and RFS (Supplementary Table).

Discussion

The present study revealed that the AFP response—namely the change of AFP 1 week after resection—is a simple and novel indicator of the oncologic effect of surgical treatment of HCC, predicts survival of patients and tumor recurrence independently of the tumor-related risk factors, and can be obtained shortly after resection.

The efficacy of surgical resection is determined by the tumor biology and thoroughness of the resection. Many studies have focused on tumor biology based on the clinical features and molecular profiles of tumors, and the thoroughness of resection is usually evaluated by traditional imaging techniques. Imaging techniques may not be sensitive and accurate enough, however, to detect occult lesions in the remnant liver a short time after resection. An ideal examination of the thoroughness of resection should be reproducible, objective, inexpensive, and easy to use.

Loss of serum AFP within 1 month after a resection has been found to be a relatively reliable predictor of tumor recurrence and survival.[33,34] Patients with AFP loss within 1 month, referred to in an earlier study as AFP complete resolution (early AFP CR),[35] had a better OS and RFS compared with those whose AFP were still above the normal level 1 month after surgery. However, the present study showed that, of the patients with early AFP CR, the AFP nonresponders had similar survival rates as the patients whose AFP level did not return to normal level 1 month after resection. These findings suggest that AFP response was a more sensitive marker for evaluating patient survival and tumor recurrence than early AFP CR.

Many studies and guidelines have noted that patients having a single tumor with microvascular invasion or multiple tumors have a higher risk of postoperative HCC recurrence.[38,39,41] The present study showed that AR is an indicator of patient survival and risk of tumor recurrence, which is independent of the commonly used markers based on a combination of tumor factors. The RFS of AFP nonresponders with a low risk of tumor recurrence was similar to that of patients with a high risk of tumor recurrence, implying the necessity of complete removal of tumor burdens even in patients with a low risk of tumor recurrence. For patients with a high risk of tumor recurrence, AFP nonresponders had much poorer RFS than AFP responders, suggesting a higher risk of tumor recurrence, and adjuvant therapy should be considered. A previous study demonstrated that HCC patients with

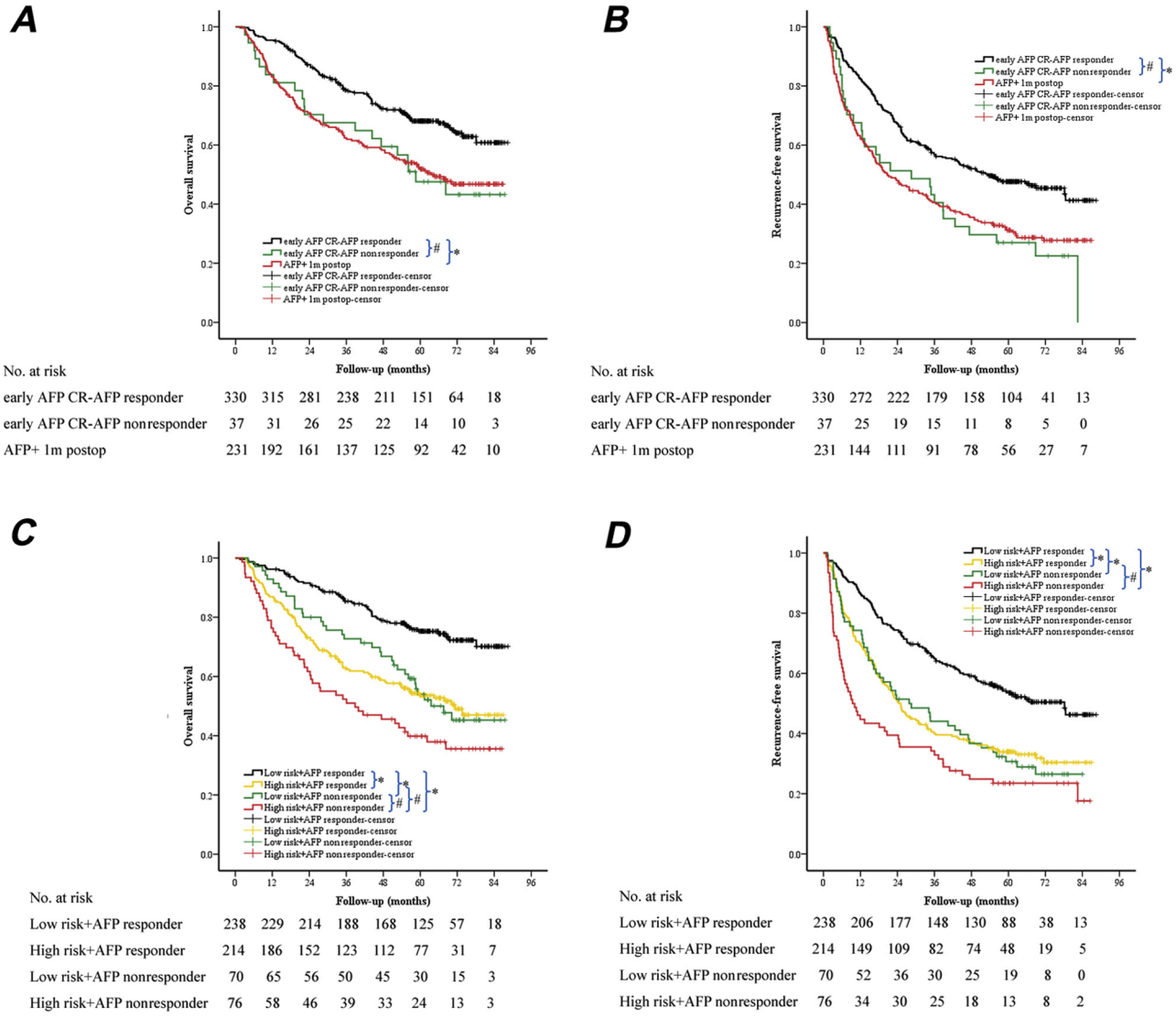

Fig 3. Kaplan–Meier curves for OS and RFS in HCC patients of AR combined with early AFP CR and risk of tumor recurrence. (*A* and *B*) OS and RFS in relationship with early AFP CR and AFP response. Early AFP CR, loss of serum AFP within 1 month after resection. AFP+ 1m postop, abnormal AFP level detected at 1 month after resection. $^{*}P < .001$, $^{\#}P < .05$. (*C* and *D*) OS and RFS in relationship with risk of tumor recurrence and AFP response. High risk: patients having a single tumor with microvascular invasion or multiple tumors. Low risk: patients having a single tumor without microvascular invasion. $^{*}P < 0.001$; $^{\#}P < .05$.

higher risk of postoperative recurrence might benefit from adjuvant therapy such as TACE.[38] Because we found that AR was an indicator of patient survival and tumor recurrence independent of the commonly used combination of tumor factors, AR might help to identify those needing adjuvant treatment after HCC resection.

An important limitation of this study is that AR is only used for patients with elevated AFP. Recent evidence has shown that intertumoral heterogeneity, when multiple tumor nodules were present, or even intratumoral heterogeneity in HCC,[42] may increase difficulty in predicting the oncologic response to resection by changes in AFP levels. A combination of AFP with other tumor markers, such as AFP-L3 or DCP, may improve the predictive power of the markers. Some AFP responders developed early tumor recurrence, likely caused by a small amount of residual tumor cells, especially AFP-negative tumors. We do not have complete data regarding the AFP levels in patients with recurrent tumors because many patients were not treated for tumor recurrence in our hospital. On the other hand, several AFP nonresponders did not develop early tumor recurrence. Injuries and inflammatory reaction caused by resection, subsequent liver regeneration, and liver cirrhosis may also contribute to elevating the AFP level or influence the postoperative reduction of the AFP level.[43,44] These may result in false-positive elevation of AFP and also explain the fact that some AFP responders had an abnormal AFP level at 1 month after resection. Another limitation is that AFP on day 7 was estimated by the average of the AFP values measured on day 6 and day 8 in a small number of patients. All these limitations highlight the need for a multicenter prospective study, evaluating the value of AFP response and discovering combined prognostic markers.

In conclusion, the AFP response is a novel and simple marker for the thoroughness of HCC resection and an independent predictive factor of OS and RFS after surgical resection. Given the simplicity of calculating AR and the popularity of the AFP test, AR could be a ready-to-use tool to individualize the estimated risk of incomplete tumor removal, enabling doctors to design a prompt follow-up protocol and adjuvant therapy after HCC resection, especially for AFP nonresponders.

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Conflict of interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.surg.2019.01.009.

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