

Early Prediction of Objective Response of Fibrinogen in a Real-World Cohort of Hepatocellular Carcinoma Cases Treated by Programmed Cell Death Receptor-1 and Lenvatinib

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Background: This cohort study aimed to investigate the influence of fibrinogen on progression-free survival and overall survival in unresectable HCC cases treated by PD-1 and lenvatinib.

Methods: A total of 57 unresectable HCC cases who received lenvatinib and PD-1, such as toripalimab, camrelizumab, or sintilimab, in Beijing Ditan Hospital Affiliated to Capital Medical University were enrolled in this study.

Results: Vascular invasion, high FIB ($>2.83\text{g/L}$), and metastasis were highly correlated with low PFS. There was a significant correlation between a raised risk of death and metastasis and increased FIB ($>2.83\text{g/L}$).

Conclusion: FIB is associated with outcomes of unresectable HCC cases treated by PD-1 and lenvatinib.

Keywords: FIB, lenvatinib, PD-1, prediction, hepatocellular carcinoma

Introduction

HCC (hepatocellular carcinoma) is deemed as the sixth familiar malignancy in the world and the fourth prime reason for tumor-associated death.¹ In spite of progress in previous tests, most cases of HCC are in advanced stage.² Unluckily, only systemic and/or alleviative therapy are indicated for majority of the cases in advanced stage. The mean survival time was only several months.^{3–7}

Nowadays, there are three first-line targeted therapies for late HCC, namely sorafenib, Lenvatinib, and combination of atezolizumab and bevacizumab.^{8–11} The second-line targeted treatment options include pembrolizumab and nivolumab.^{12,13} However, the second-line treatment does not contribute to significant improvement of major endpoints.¹⁴ Thus, it is necessary to explore new effective treatment modalities for cases with advanced HCC.

Combined treatments including PD-1 inhibitors are under investigation for a variety of cancer, eg, renal cell carcinoma, endometrial cancer, gastric cancer, and HCC.^{15–17} However, the per year cost of nivolumab and pembrolizumab reached \$63k USD and \$87k USD, respectively.¹⁸ The most advantage of PD-1 mAbs for Chinese cases, namely, toripalimab, camrelizumab, and sintilimab, is the remarkably low expense (approximately \$17.5k, \$17.0k and \$13.9k USD every year, respectively).¹⁸ This is the first research to investigate the efficacy

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and safety of LEN and the PD-1 inhibitors in HCC cases in the real world in China, aiming to reveal the real effects of the therapy in HCC besides clinical trial projects.¹

In recent decades, previous clinical investigations have demonstrated that fibrinogen is involved in SIRS (systemic inflammatory response syndrome) and tumorigenesis.^{19–22} During tumor progression, due to metastasis, infiltration and destruction of malignant cells, abundant pro-coagulant substances are released into the blood, leading to hyper-coagulable state.^{23–25} Ji et al reported that high plasma fibrinogen levels were significantly related to poor prognosis of cases with gastrointestinal malignant tumor.²²

Nevertheless, the correlation between FIB (fibrinogen) and prognosis in unresectable HCC patients treated with lenvatinib and PD-1 (programmed cell death receptor-1) remains to be investigated. Therefore, this cohort study aimed to investigate the influence of FIB on progression-free survival and overall survival in unresectable HCC cases treated by PD-1 and lenvatinib.

Materials and Methods

Ethics Statement

The study protocol followed the Declaration of Helsinki, and was approved by the Ethics Committee of Beijing Ditan Hospital, Capital Medical University. All the participants submitted the written informed consent form prior treatment.

Patients

From Jan. 2020 to Dec. 2020, 57 unresectable HCC cases who received lenvatinib and PD-1, such as toripalimab, camrelizumab, or sintilimab, in Beijing Ditan Hospital Affiliated to Capital Medical University were enrolled in this study. All the cases conformed to the radiologically or histologically diagnostic criteria for HCC. HCC was staged according to the BCLC (Barcelona Clinic Liver Cancer) stage.²⁶

Eligible criteria: 1) available baseline FIB data; 2) Lenvatinib and PD-1 treatment for over one cycle; 3) followed up for over 4 weeks; 4) complete clinical and laboratory data; 5) no lost follow-up.

Exclusion criteria: 1) cases who received blood transfusions or regularly took anticoagulant or procoagulant drugs within 1 month; 2) cases with concomitant diseases which may affect plasma coagulation levels (ie, pulmonary embolism, VTE, or DIC (disseminated intravascular coagulation)

within 1 month or during the subsequent treatment); 3) other hematological diseases or malignancies.

The results of laboratory tests within 1 week prior to combination treatment were harvested from the medical records. The data of FIB, AFP (alpha-fetoprotein), ALB (albumin), P-ALB (pre-albumin), HCY (homocysteine), and GGT (gamma-glutamyl transpeptidase) were analyzed.

Treatment

According to physician's assessment on drug tolerance for HCC cases with older age, non-Child–Pugh A, light body weight and hydrothorax, ascitic fluid, or gastrointestinal varicose veins with a bleeding potential, LEN was taken orally at a starting dose of 12 mg (n=12), 10 mg (n=3), 8mg (n=31), and 4 mg (n=11). CAM, TOR or SIN was given at a dose of 200 mg every 3 weeks.

AEs (adverse events) were estimated by using CTCAE (Common Terminology Criteria for Adverse Events) V.4.03.²⁷ According to the manufacturer manual, if treatment-related AEs appeared, dose was temporarily interrupted or decreased until the symptom was resolved to grade 1 or 2. According to the drug manufacturer's guidelines, the dose was reduced or treatment was interrupted when a patient developed any grade ≥ 3 LUN/PD-1 severe AEs or if any unacceptable treatment-related AEs occurred.

Follow-Up, PFS (Progression-Free Survival), and OS (Overall Survival)

The cases were followed up regularly until March 2021 by telephone, emails or medical records, with a frequency of once every 4 weeks. Therapeutic response was assessed by using a triphasic scanning technique, MRI, or CT according to mRECIST (modified RECIST).²⁸

The major end points were OS and PFS. OS was defined as the interval between the beginning of LEN/CAM or SIN or TOR combination treatment and the deadline or the time of death. PFS was defined as the interval between the beginning of LEN/CAM or SIN or TOR combination treatment and the time of disease progression or relapse as stated in mRECIST or death.

Statistical Analysis

SPSS 22.0 software (IBM; SPSS Inc) was introduced for data analysis. Continuous variables were expressed as medians (interquartile range), and categorized using median values as cut-off point. Cox proportional hazards regression models were introduced for univariate and

multivariate analyses of clinical variables. Kaplan–Meier survival curves were plotted using GraphPad Prism 7.0 (GraphPad Software Inc), with involvement of proportional hazard model and the Log rank test. Chi-square test was used to analyze the correlation between FIB and clinical features. $p < 0.05$ indicated significant difference.

Results

Patient Features

The main baseline features of the subjects enrolled are listed in Table 1. In this study, 48 (84.21%) cases were males and 9 (15.79%) were females. The median age was 58 years (range 29–79). Liver cirrhosis, which was diagnosed with biopsy or the imaging techniques, was confirmed in 47 (82.46%) cases. Regarding liver function of the cases, 80.7% and 19.3% were of Child–Pugh grade A and B, respectively. The median value for FIB was 2.83g/L, which was used as the cut-off point. The important indicator in the diagnosis of HCC was 400 ng/mL, which was used as the thresholds. All cases were prescribed lenvatinib and PD-1. According to the BCLC system, before PD-1 and lenvatinib therapy, 11 (19.30%) and 46 (80.70%) cases were of BCLC stage B and C HCC, respectively. Lymph-node metastasis, venous metastasis, lung metastasis, bone metastasis, and other metastases affected 5, 29, 5, 4, and 8 cases, respectively. All 57 cases were given the combination therapy of LEN and PD-1,

sintilimab (n=30), camrelizumab (n=25) and toripalimab (n=2). Regarding the previous systemic treatment, 9 cases were ever treated by MKI therapy (sorafenib, n=8; lenvatinib, n=1). During the follow-up period (median, 9.8 months), 11 (19.29%) cases developed tumor progression and 5 (8.77%) cases died.

Therapeutic Response and Adverse Events

According to mRECIST for radiological responses, CR was achieved in 3 cases (5.26%), PR in 26 cases (45.61%), and SD in 13 cases (22.81%). The ORR rate and DCR rate were 50.88% and 73.68%, respectively (Table 2).

Cumulative progression-free survival at 5, 10 and 15 months was 71.21%, 23.74% and 16.43%, respectively (Figure 1A). Cumulative overall survival at 5, 10 and 15 months was 89.27%, 52.83% and 34.62%, respectively (Figure 1B).

In this study, 96% of the cases experienced an AE, and 39% of the patients had grade ≥ 3 treatment-related AEs (Table 3). The most common treatment-related AEs of any grade (Table 3) were hypertension (42.11%), diarrhea (38.6%), decreased appetite (31.58%), hypothyroidism (29.82%), elevated liver enzymes (28.07%) and fatigue (31.58%). The most common treatment-related AEs of grade 3 were hypertension (7.02%), proteinuria (5.27%), diarrhea (5.27%) and fatigue (5.27%). Dose was reduced in 7 (12.28%) patients due to AEs.

Table 1 Characteristics of HCC Cases (n = 57)

Parameters	No. of Patients
Gender (female/male)	9/48
Age (years)	58 (51,64)
Tumor diameter (cm)	6 (4,8.9)
Tumor number (solitary/multiple)	21/36
Vascular invasion (no/yes)	28/29
Fibrinogen (g/L)	2.83(2.45,3.39)
AFP (ng/mL)	202.37(6.65,1766.88)
ALB (U/L)	37.3 (34.9,40.3)
P-ALB (mg/L)	114.9 (69.7,181.1)
HCY (umol/L)	14.1(11.4,16.6)
GGT (U/L)	81.9(41.7,144.1)
Child–Pugh class (A/B)	46/11
Etiology (HBV/HCV/Alcohol)	49/4/4
BCLC stage (B/C)	11/46
Metastasis sites	
Lung	5
Lymph nodes	5
Bone	4
Other	8

The Relationship of Fibrinogen with Clinicopathologic Features of Unresectable HCC Cases

The relationship of fibrinogen with clinicopathological features of HCC cases is shown in Table 4. There was a significant correlation between fibrinogen levels and vascular invasion ($P=0.005$), tumor diameter ($P=0.001$), and GGT ($P=0.047$) in HCC cases.

Table 2 Efficacy Response Based on mRECIST

	FIB (g/L)	
	≤ 2.83	> 2.83
CR	3	0
PR	13	13
SD	9	9
PD	4	6
ORR	55.17%	46.43%
DCR	86.21%	78.57%

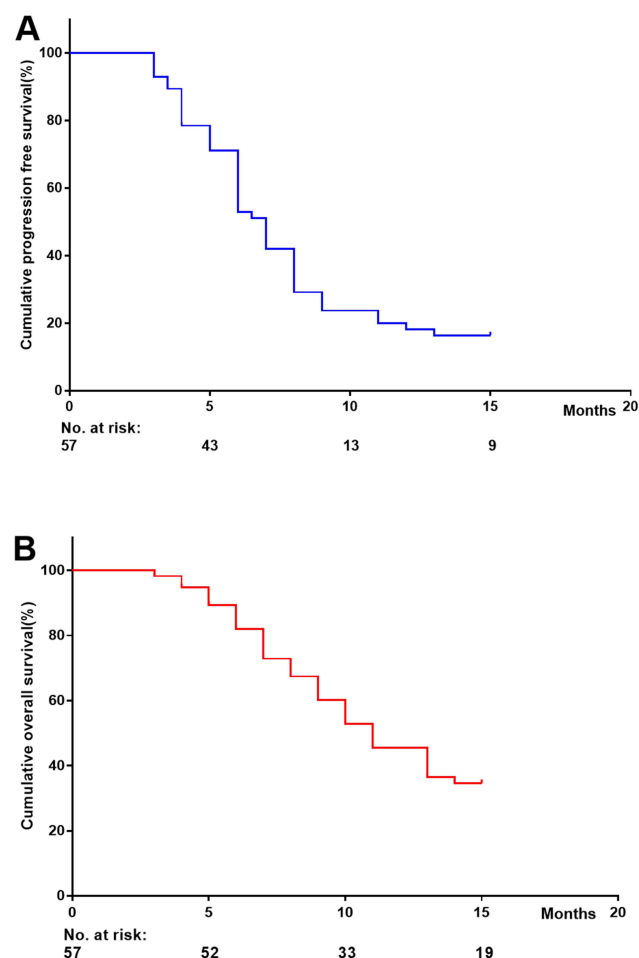


Figure 1 Progression-free survival (A) and overall (B) survival curves based on mRECIST.

Prognostic Value of FIB for Progression-Free Survival and Overall Survival

In the cohort study, the Kaplan–Meier curve was plotted with involvement of Log rank test and Cox proportion regression model, and the prognostic roles of FIB in

HCC patients were investigated. As shown in Figure 2, FIB (>2.83 g/L) was negatively correlated with progression-free survival and overall survival, respectively.

Vascular invasion (unadjusted HR=1.877, 95% CI=1.049–3.358; adjusted HR=2.297, 95% CI=1.254–4.209), high FIB (>2.83 g/L; unadjusted HR=1.845, 95% CI=1.032–3.295; adjusted HR=1.987, 95% CI=1.096–3.603), and metastasis (unadjusted HR=1.948, 95% CI=1.081–3.510; adjusted HR=2.035, 95% CI=1.114–3.718) were highly correlated with low PFS (Table 5).

There was a significant correlation between a raised risk of death and metastasis (unadjusted HR=1.937, 95% CI=1.083–3.462; adjusted HR=2.093, 95% CI=1.164–3.764) and increased FIB (unadjusted HR=2.068, 95% CI=1.156–3.701; adjusted HR = 1.963, 95% CI=1.091–3.530) (Table 6).

Discussion

Despite advance in the diagnosis and treatment of HCC, the 5-year OS rate of HCC case remains unfavorable.¹ Of note, the 5-year survival rate of HCC cases who were treated appropriately after early diagnosis was over 50%, indicating that HCC mortality can be reduced by early screening.

In the current study, the prognosis of unresectable HCC cases with high FIB was poorer compared to those with low FIB after treated by PD-1 and lenvatinib. After adjusted for FIB, vascular invasion and metastasis, multivariate analysis demonstrated that FIB was independently correlated with OS and PFS. And metastasis was also an independent predicting factor of OS. Moreover, vascular invasion and tumor metastasis was also independently associated with PFS of the cases. The findings above indicated that FIB was associated with both OS and PFS in unresectable HCC cases after PD-1 and Lenvatinib treatment. Our evidence showed that higher FIB was

Table 3 Treatment-Related Adverse Events

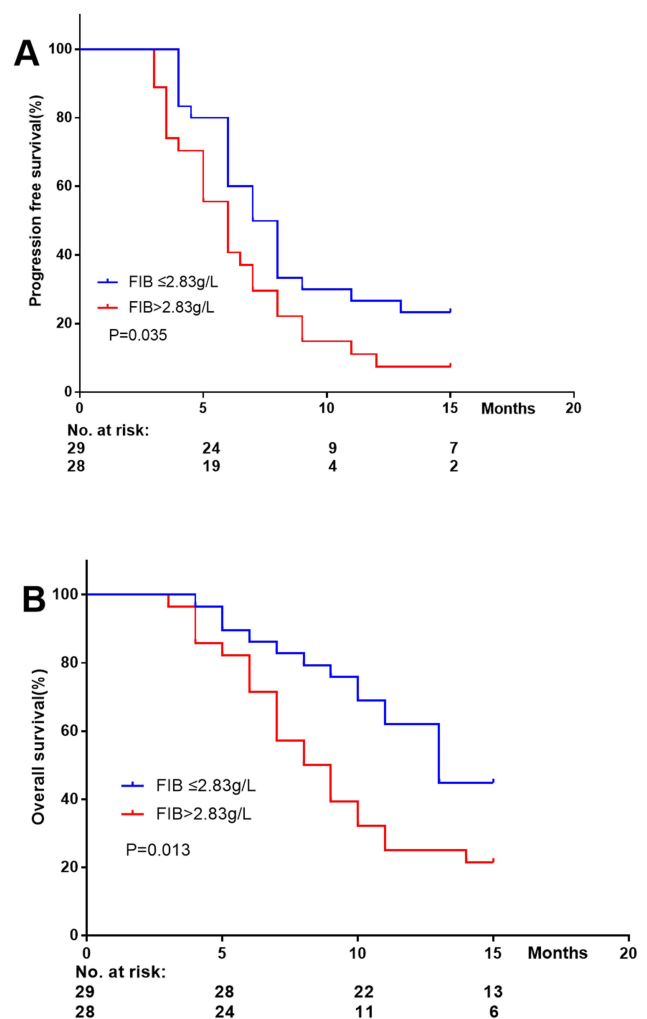
Treatment-Emergent Adverse Events	Any Grade	Grade 1	Grade 2	Grade ≥ 3
Hypertension	24 (42.11%)	9(15.79%)	11(19.3%)	4(7.02%)
Fatigue	15 (26.32%)	5(8.77%)	7(12.28%)	3(5.27%)
Decreased appetite	18 (31.58%)	10(17.54%)	8(14.04%)	0
Hypothyroidism	17 (29.82%)	11 (19.3%)	5(8.77%)	1(1.75%)
Proteinuria	10 (17.54%)	6 (10.53%)	3(5.27%)	3(5.27%)
Palmar–plantar erythrodysesthesia syndrome	11(19.3%)	6 (10.53%)	4(7.02%)	1(1.75%)
Elevated liver enzymes	16(28.07%)	8(14.04%)	6 (10.53%)	2(3.51%)
Diarrhea	22(38.6%)	13(22.81%)	6 (10.53%)	3(5.27%)
Adrenocortical function decreased	1(1.75%)	0	0	1(1.75%)
Rash	7(12.28%)	4(7.02%)	2(3.51%)	1(1.75%)

Table 4 Relationship Between FIB and the Clinical Characteristics of HCC Patients

Variables	Fibrinogen (g/L)		χ^2	P
	≤ 2.83	> 2.83		
Gender				
Male	24	24	0.09	0.76
Female	5	4		
Age (years)				
≤ 60	16	17	0.18	0.67
> 60	13	11		
Cirrhosis				
No	6	4	0.404	0.525
Yes	23	24		
Tumor diameter (cm)				
≤ 5	17	4	12.034	0.001
> 5	12	24		
Tumor number				
Single	10	9	0.035	0.851
Multiple	19	19		
Vascular invasion				
No	9	19	7.729	0.005
Yes	20	9		
AFP (ng/mL)				
≤ 400	14	17	0.888	0.346
> 400	15	11		
Pre-ALB (mg/L)				
≤ 100	13	13	0.015	0.903
> 100	16	15		
ALB (g/L)				
≤ 35	7	8	0.144	0.704
> 35	22	20		
GGT (U/L)				
≤ 60	11	18	3.959	0.047
> 60	18	10		
HCY (umol/L)				
≤ 15	21	15	2.174	0.14
> 15	8	13		
Child-Pugh class				
A	24	22	0.16	0.689
B	5	6		
BCLC stage				
B	6	5	0.073	0.786
C	23	23		

positively correlated with tumor diameter, vascular invasion, GGT in HCC.

It has been shown that hyperfibrinogenemia is correlated with poor prognosis of cases with a variety of tumors, but the mechanism remain to be investigated.

**Figure 2** Kaplan-Meier curves of FIB for PFS (A) and OS (B).

The adhesion of tumor cells to platelets is facilitated by fibrinogen, causing platelet aggregation around the tumor cells, and immune attack may be prevented.²⁹ The metastasis, invasion and proliferation of tumor cells are regulated by fibrinogen via binding to growth factors, eg, PDGF (platelet-derived growth factor), FGF-2 (fibroblast growth factor-2), and VEGF (vascular endothelial growth factor).^{30–32} Tumor progression is shown to be related to inflammatory response, that's, leukocyte infiltration in the tumor matrix, and fibrinogen is converted to fibrin, thereby promoting tumor angiogenesis.³³ Also, EMT (epithelial-mesenchymal transition) of tumor cells is facilitated by fibrinogen, which also promotes tumor metastasis and invasion.¹⁹ Our study indicated that changes of the tumor microenvironment and inflammatory response of HCC may be reflected by FIB, a new prognostic index before surgery.

Table 5 Progression-Free Survival Analysis

Variables	Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	P
Gender (Male/Female)	0.934	0.436–2.002	0.861			
Age, years (≤ 60 / > 60)	0.999	0.972–1.028	0.966			
Cirrhosis (No/Yes)	0.412	0.319–1.598	0.412			
Tumor diameter, cm (≤ 5 / > 5)	0.985	0.543–1.78	0.96			
Tumor number (single/multiple)	1.103	0.824–1.246	0.902			
Vascular invasion (No/Yes)	1.877	1.049–3.358	0.034	2.297	1.254–4.209	0.007
AFP, ng/mL (≤ 400 / > 400)	0.912	0.513–1.621	0.753			
Fibrinogen, g/L (≤ 2.83 / > 2.83)	1.845	1.032–3.295	0.038	1.987	1.096–3.603	0.024
P-ALB, g/L (≤ 100 / > 100)	0.819	0.460–1.455	0.495			
Metastasis (No/Yes)	1.948	1.081–3.510	0.026	2.035	1.114–3.718	0.021
GGT, U/L (≤ 60 / > 60)	1.745	0.645–3.237	0.075			
HCY, umol/L (≤ 15 / > 15)	0.847	0.465–1.542	0.587			
Child–Pugh class (A/B)	0.647	0.288–1.452	0.292			
BCLC stage (B/C)	1.144	0.552–2.368	0.718			

Table 6 Overall Survival Analysis

Variables	Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	P
Gender (Male/Female)	0.982	0.457–2.111	0.963			
Age, years (≤ 60 / > 60)	0.999	0.972–1.026	0.917			
Cirrhosis (No/Yes)	0.816	0.364–1.825	0.62			
Tumor diameter, cm (≤ 5 / > 5)	0.921	0.508–1.671	0.787			
Tumor number (single/multiple)	1.079	0.881–1.322	0.46			
Vascular invasion (No/Yes)	1.559	0.878–2.769	0.131			
AFP, ng/mL (≤ 400 / > 400)	0.884	0.498–1.571	0.675			
Fibrinogen, g/L (≤ 2.83 / > 2.83)	2.068	1.156–3.701	0.014	1.963	1.091–3.530	0.024
P-ALB, g/L (≤ 100 / > 100)	1.001	0.563–1.777	0.999			
Metastasis (No/Yes)	1.937	1.083–3.462	0.026	2.093	1.164–3.764	0.014
GGT, U/L (≤ 60 / > 60)	1.554	0.841–2.873	0.159			
HCY, umol/L (≤ 15 / > 15)	0.916	0.505–1.662	0.772			
Child–Pugh class (A/B)	0.513	0.229–1.154	0.107			
BCLC stage (B/C)	1.206	0.583–2.495	0.614			

Wang et al³⁴ analyzed 538 HCC cases, and found that FIB ≥ 2.83 g/L (HR 2.051, 95% CI 1.093–3.851; HR 1.660, 95% CI 1.124–2.451) was independently associated with OS and DFS (disease-free survival). Similarly, Dai et al³⁵ analyzed 302 HCC cases, and found that FIB > 4 g/L (HR 2.158, 95% CI 1.427–3.263; HR 2.161, 95% CI 1.429–3.267) was independently associated with OS and DFS. In our cohort study, it was also found that FIB > 2.83 g/L (HR 1.987, 95% CI 1.096–3.603; HR 1.9637, 95% CI 1.091–3.530) was independently associated with PFS and OS of HCC cases treated by lenvatinib (a new targeted drug) and domestically developed PD-1 (sintilimab, camrelizumab,

toripalimab). Although there was a bit difference in the treatment in the reports of Wang et al³⁴ and Dai et al,³⁵ a greater number of enrolled patients in the real clinical setting is the advantage of our study. Our study was clinically significant since associated predictive indicators of unresectable HCC cases treated by PD-1 and lenvatinib were identified.

However, there are also some limitations. First, the sample size of this study is small since it is a single-center investigation. Second, we did not analyze the treatment of HCC subsequent to PD-1 and lenvatinib therapy, which may also affect prognosis. In addition, we did not

analyze the treatment of HCC these drugs with lenvatinib therapy, respectively, which may also affect prognosis. The findings of the treatment of HCC lenvatinib therapy in our study remain to be further verified by well-designed studies of with a larger sample size, respectively.

Conclusion

Our study found that FIB is associated with outcomes of unresectable HCC cases treated by PD-1 and lenvatinib. However, the potential roles of FIB in identification of high-risk HCC cases and evaluation of individualized treatment remain to be explored.

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Disclosure

Yanjun Shen and Huige Wang are co-first authors for this study. The authors declare no competing conflicts of interest in this paper.

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