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ORIGINAL RESEARCH

The Prognostic Role of Circulating FPR Before Operation in Patients with BCLC A-C Hepatocellular Carcinoma: A Retrospective Cohort Study

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Background: This research aimed to comprehensively assess the prognostic role of fibrinogen to prealbumin ratio (FPR) in BCLC A-C HCC patients treated by TACE and RFA.

Methods: The research included 240 patients at stage BCLC A-C treated by TACE and RFA at Beijing Ditan Hospital of Capital Medical University from May 2011 to November 2018.

Results: The results showed that the size of the tumor, vascular invasion, α-foetoprotein, cirrhosis, NLR, LMR, and PLR showed prognostic value in predicting 5-year OS. Besides, FPR (95% confidence interval: 1.006–1.013, hazard ratio: 1.009) was a prognostic factor for the prediction of 5-year OS in HCC.

Conclusion: Our research indicated that FPR was a potential indicator for patients with BCLC A-C hepatocellular carcinoma after treatment of RFA and TACE.

Keywords: FPR, hepatocellular carcinoma, prognosis, overall survival

Introduction

As the 6th most prevalent tumor in the world, hepatocellular carcinoma (HCC) ranks the 3rd among all the causes of malignancy-associated death in China.[1,2] Only 30–40% of HCC patients could gain benefits from conventional therapies, including locoregional treatments, liver transplantation, and hepatic resection.[3] It is of great necessity to discover novel prognostic markers for individualized treatment. Currently, serum alpha fetalprotein (AFP) is the most common serological diagnostic tumor marker for HCC. Serum markers could be used in the prediction of HCC survival and recurrence since they could be easily obtained at a low cost.[4]

Previous research demonstrated that fibrinogen (Fib) and its corresponding peptides could promote inflammation in malignancies.[5] Furthermore, accumulating findings showed that increased Fib was related to worse OS and survival without tumor.[6,7] Except for Fib, prealbumin (pAlb), a factor indicating nutritional status, can also be independently used in predicting prognosis. A decreased level of pAlb before operation indicates a poor result of survival.[8,9] Therefore, combined use of FPR, Fib and pAlb could provide more reliable results on the nutrition and inflammation status of the patients and might be used as a prognostic factor.

To date, a limited number of research focused on the role of FPR in HCC prognosis after treated by TACE and RFA. In our research, the effects of FPR on overall survival in BCLC A-C HCC patients treated by TACE and RFA were explored.

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Table 1 Clinical and Pathological Features

Variables	No. of Patients
Male/female	200/40
Age (years)	59(52,68)
Tumor diameter (cm)	4(2.9,6.6)
Tumor number (1/≥2)	145/95
Vascular invasion (No/Yes)	182/58
Fibrinogen (g/L)	261(211.25,333.25)
ALB (U/L)	35.03±6.50
P-ALB (mg/L)	104.38±59.16
AFP (ng/mL)	43.8(8.63,349.5)
CEA	3.45(2.2,5.0)
PNI	41.22±7.87
NLR	2.27(1.47,3.67)
LMR	2.91(1.93,3.76)
PLR	84.98(57.71,136.58)
Cirrhosis (No/Yes)	40/200
Child-Pugh grade (A/B)	153/87
Etiology (HBV/HCV/Alcohol)	205/25/12
BCLC stage (A/B/C)	125/50/65
Metastasis sites	
Lung	10
Lymph nodes	6
Bone	1
Other	3

Abbreviations: ALB, albumin; P-ALB, prealbumin; AFP, alpha-fetoprotein; CEA, carcinoembryonic antigen; PLR, platelet/lymphocyte ratio; NLR, neutrophil/lymphocyte ratio; LMR, lymphocyte/monocyte ratio; PNI, albumin (g/L)+ 5× lymphocyte (109 /L); HBV, Hepatitis B Virus; HCV, Hepatitis C Virus; BCLC, Barcelona Clinic Liver Cancer.

Materials and Methods

Patient Selection

The experiment protocol was approved by the Ethics Committee of Beijing Ditan Hospital, Capital Medical University. Our research strictly abided by the Declaration of Helsinki. Informed consent was signed by all participants prior to the treatment.

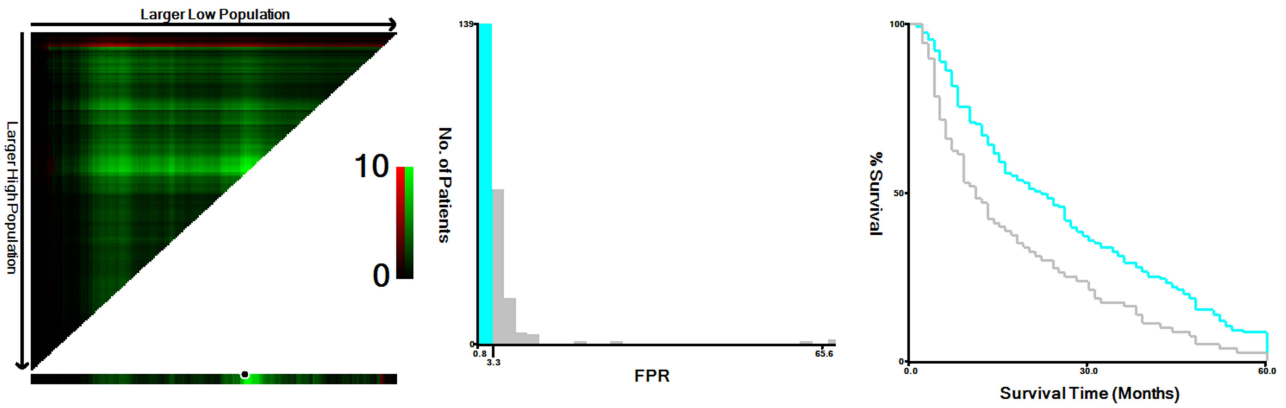

Figure 1 The ideal cut-off value of FPR in HCC calculated by X-title software.
Note: The ideal cut-off value, 3.3, was identified by locating the most obvious pixel on the X-tile plot.
Abbreviation: FPR, fibrinogen/prealbumin ratio.

Table 2 Correlation Between Clinical Characteristics and FPR in 240 Subjects with HCC

Variable	FPR		χ^2 /t	P
	Low (n=151)	High (n=89)		
Sex				
Male	124	76	0.432	0.511
Female	27	13		
Tumor diameter (cm)				
≤5	104	50	3.924	0.048
>5	47	39		
Tumor number				
1	95	50	1.062	0.303
≥2	56	39		
Vascular invasion			2.939	0.086
No	120	62		
Yes	31	27		
AFP (ng/mL)			0.173	0.677
≤400	117	71		
>400	34	18		
Cirrhosis			0.004	0.952
No	25	15		
Yes	126	74		
Child-Pugh grade			10.647	0.001
A	108	45		
B	43	44		
BCLC stage				
A	88	37	7.293	0.026
B	30	20		
C	33	32		
Age (years)	60.56±10.91	58.45±9.39	1.97	0.129
CEA	4.31±5.57	4.03±2.73	0.479	0.658
NLR	3.01±2.97	3.26±2.74	0.053	0.529
PLR	118.09±11.42	103.21±7.76	0.864	0.407
LMR	3.31±1.85	2.66±1.43	0.689	0.407
PNI	42.82±8.23	38.49±6.39	6.53	0.011

Abbreviations: AFP, alpha-fetoprotein; CEA, carcinoembryonic antigen; FPR, fibrinogen/prealbumin ratio; PNI, albumin (g/L)+ 5× lymphocyte (109 /L); PLR, platelet/lymphocyte ratio; NLR, neutrophil/lymphocyte ratio; LMR, lymphocyte/monocyte ratio; BCLC, Barcelona Clinic Liver Cancer.

In this study, 240 patients at stage BCLC A-C treated by TACE and RFA at Beijing Ditan Hospital of Capital Medical University from May 2011 to November 2018 were analyzed. The clinicopathological features were recorded according to the criteria of the American Association for the Study of Liver Disease.[10]

Inclusion criteria: (1) liver function before operation: Child-Pugh Class A or Class B; (2) without immunity-associated or hematological diseases; (3) without other kinds of malignancies; (4) without infectious diseases except for hepatitis B or C; and (5) preoperative FPR collected <1 week before treatment.

Exclusion criteria: (1) critical diseases, such as hepatic or heart failure; (2) gastric variceal or esophageal hemorrhage within 1 month; (3) severe coagulation disorders, (4) neoadjuvant/adjuvant chemoradiotherapy.

Clinical Parameters and Laboratory Results

Based on the medical record of the patient, the basic information was collected (number of tumors, the maximum diameter of the tumor (cm), sex, Child-Pugh classification, age, presence of liver cirrhosis, AFP concentration in serum, Fib, serum CEA, prealbumin (PA), count of platelets, lymphocytes, monocytes, and neutrophils, presence of thrombosis

Table 3 Correlation Between Clinical Characteristics and FPR in BCLC a

Variable	Case (125)	FPR		χ^2 /t	P
		Low (n=88)	High (n=37)		
Sex					
Male		69	28	0.112	0.738
Female		19	9		
Tumor diameter (cm)					
≤5		83	36	0.562	0.669
>5		5	1		
Tumor number					
1		66	28	0.006	0.936
2		22	9		
AFP (ng/mL)					
≤400		75	36	3.785	0.052
>400		13	1		
Cirrhosis					
No		14	2	2.965	0.146
Yes		74	35		
Child-Pugh grade					
A		61	17	6.065	0.014
B		27	20		
Age (years)	60.65±10.15	61.66±10.76	58.24±8.17	3.5	0.061
CEA	4.13±2.87	4.17±2.98	4.04±2.38	0.056	0.814
NLR	4.29±3.02	2.74±1.31	2.90±2.21	0.1	0.919
PLR	106.04±48.38	112.86±73.82	89.79±49.02	0.136	0.245
LMR	3.36±1.82	3.56±1.90	2.88±1.54	0.041	0.839
PNI	41.14±7.83	42.63±8.08	37.67±5.99	4.024	0.047

Abbreviations: AFP, alpha-fetoprotein; CEA, carcinoembryonic antigen; FPR, fibrinogen/prealbumin ratio; PNI, albumin (g/L)+ 5× lymphocyte (109 /L); PLR, platelet/lymphocyte ratio; NLR, neutrophil/lymphocyte ratio; LMR, lymphocyte/monocyte ratio; BCLC, Barcelona Clinic Liver Cancer.

in portal vein tumor). We collected peripheral blood from the patients between 7:30–9:30 am in 1 week before combination treatment. FPR, PLR, LMR and NLR refer to fibrinogen/prealbumin, platelet/lymphocyte, lymphocyte/monocyte, and neutrophil/lymphocyte ratios, respectively. Prognostic nutritional index (PNI)= albumin (g/L)+ 5× lymphocyte (10^9 /L).

The Follow-Ups and OS (Overall Survival)

The regular follow-ups were performed every 4 weeks through medical records, emails and telephone call until November 2021. The CT, MRI, or triphasic scanning technique was used to evaluate the therapeutic effects based on mRECIST (modified RECIST).[11] The main end point in our research was OS, which was defined as the interval between diagnosis and the last follow-up or death.

Statistics

The data were analyzed using IBM SPSS 22.0 statistical software (SPSS Inc) and R version 3.2.3. Figures and survival curves were generated by using GraphPad Prism 6.0. The optimal threshold value for FPR was calculated based on the 5-year OS, and X-tile software version 3.6.1 was used. Chi-square or Student's *t*-test was used to compare the differences. Survival rate differences were assessed by using Log rank test and Kaplan–Meier curve. Cox proportional hazards model was used to conduct survival analysis and identify possible prognosis-related factors. If $p < 0.05$, the difference was regarded as statistically significant.

Results

The Characteristics of the Patients

The characteristics of 240 patients at baseline are listed in Table 1. Two hundred (83.33%) cases were male and 40 (16.67%) female. They were aged 59 years on average (range, 35–87 years). A total of 200 (200%) cases were diagnosed with liver cirrhosis. According to Child-Pugh classification, a total of 153 (63.75%) patients were scored as grade A and 87 (36.25%) patients as grade B prior to the treatment of RFA and TACE. Fifty-eight (24.17%) patients had thrombosis in the portal vein. Lung metastasis, metastasis into lymph nodes, metastasis to bones, and other types of metastases were observed in 10, 6, 1, and 3 cases, respectively.

The results showed that the ideal cut-off value was 3.3 for FPR (Figure 1). According to the cut-off value, the patients included in his study were assigned into low and high subgroups according to each biomarker. FPR was markedly related to Child-Pugh grade (p = 0.001), tumor diameter (p = 0.048), BCLC stage (p = 0.026), and PNI (p = 0.011) (Table 2). FPR was remarkably related to Child-Pugh grade (p = 0.014), and PNI (p = 0.047) (Table 3). FPR was remarkably related to Child-Pugh grade (p = 0.043), and LMR (p = 0.013) (Table 4). FPR was markedly related to LMR (p=0.028) (Table 5).

Survival Curves Between High and Low FPR

Up to the last day of the follow-up, there were 203 deaths in this study. Kaplan–Meier method and Log rank test were used to compare the survival curve between high and low FPR. The cumulative overall survival at 10, 20, 30, 40, 50, and 60 months was 62.5%, 42.91%, 29.58%, 19.58%, 11.25%, and 6.25%, respectively (Figure 2A). In Figure 2B, the high FPR (>3.3) was related to poor 5-year OS. Additionally, we compared the survival curves according to pathological phases.

Table 4 Correlation Between Clinical Characteristics and FPR in BCLC B

Variable	Case (50)	FPR		χ^2 /t	P
		Low (n=30)	High (n=20)		
Sex					
Male		26	19	1.007	0.636
Female		4	1		
Tumor diameter (cm)					
≤5		12	6	0.225	0.635
>5		21	14		
Tumor number					
1		10	4	1.058	0.304
≥2		20	16		
AFP (ng/mL)					
≤400		22	14	0.066	0.797
>400		8	6		
Cirrhosis					
No		8	6	0.066	0.797
Yes		22	14		
Child-Pugh grade					
A		22	9	4.089	0.043
B		8	11		
Age (years)	60.76±9.55	60.90±9.77	60.55±9.44	0.01	0.985
CEA	4.04±2.69	4.17±2.67	3.94±2.80	0.09	0.766
NLR	2.86±1.45	3.03±1.40	2.61±1.51	0.009	0.925
PLR	101.42±57.39	115.20±59.24	80.75±48.88	0.699	0.407
LMR	4.71±2.97	2.75±0.77	2.97±1.53	6.36	0.013
PNI	40.97±7.30	42.17±7.41	39.18±6.94	0.171	0.681

Abbreviations: AFP, alpha-fetoprotein; CEA, carcinoembryonic antigen; FPR, fibrinogen/prealbumin ratio; PNI, albumin (g/L)+ 5× lymphocyte (109 /L); PLR, platelet/lymphocyte ratio; NLR, neutrophil/lymphocyte ratio; LMR, lymphocyte/monocyte ratio; BCLC, Barcelona Clinic Liver Cancer.

Table 5 Correlation Between Clinical Characteristics and FPR in BCLC C

Variable	Case (65)	FPR		χ^2 /t	P
		Low (n=33)	High (n=32)		
Sex					
Male		29	29	0.128	0.721
Female		4	3		
Tumor diameter (cm)					
≤5		12	7	2.288	0.130
>5		21	25		
Tumor number					
1		19	18	0.012	0.914
≥2		14	14		
Vascular invasion					
No		2	5	1.547	0.214
Yes		31	27		
AFP (ng/mL)					
≤400		20	21	0.176	0.675
>400		13	11		
Cirrhosis					
No		3	7	2.040	0.153
Yes		30	25		
Child-Pugh grade					
A		25	19	1.994	0.158
B		8	13		
Age (years)	57.35±11.26	57.33±11.95	55.37±10.68	0.569	0.453
CEA	4.46±2.87	4.82±1.69	4.09±2.12	0.921	0.341
NLR	3.89±3.30	3.73±3.02	4.07±3.62	0.034	0.855
PLR	133.72±88.88	134.67±81.09	132.75±97.57	0.111	0.740
LMR	2.68±1.84	3.14±2.26	2.22±1.12	5.076	0.028
PNI	41.55±8.47	44.01±9.41	39.01±6.59	3.179	0.079

Abbreviations: AFP, alpha-fetoprotein; CEA, carcinoembryonic antigen; FPR, fibrinogen/prealbumin ratio; PNI, albumin (g/L)+ 5× lymphocyte (109 /L); PLR, platelet/lymphocyte ratio; NLR, neutrophil/lymphocyte ratio; LMR, lymphocyte/monocyte ratio; BCLC, Barcelona Clinic Liver Cancer.

In BCLC C (Figure 3F), higher FPR was remarkably related to poorer 5-OS (p = 0.01) compared with lower FPR. The cumulative overall survival at 10, 20, 30, 40, 50, and 60 months was 41.53%, 21.53%, 12.31%, 6.15%, 1.54%, and 1.54%, respectively (Figure 3E). In BCLC A (Figure 3B) and B (Figure 3D), higher FPR showed a worse result in survival compared with

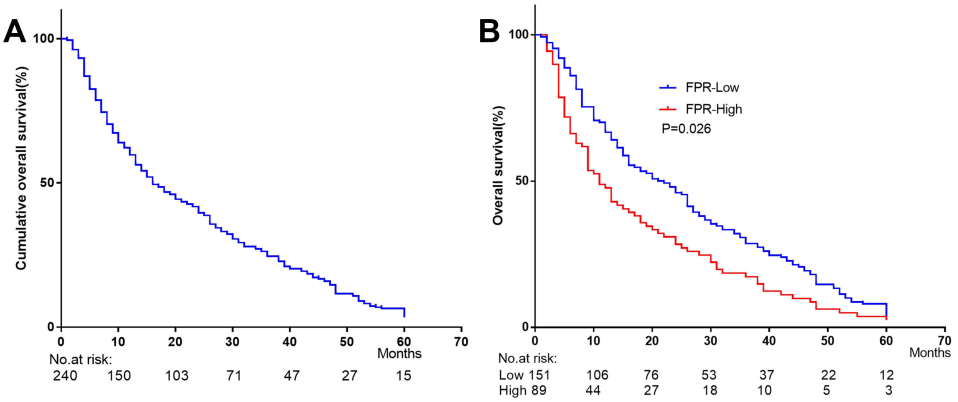

Figure 2 5 years' OS in 240 subjects with HCC.
Note: Cumulative overall survival curve (**A**) and Kaplan–Meier curves of FPR for 5-year OS (**B**).
Abbreviation: FPR, fibrinogen/prealbumin ratio.

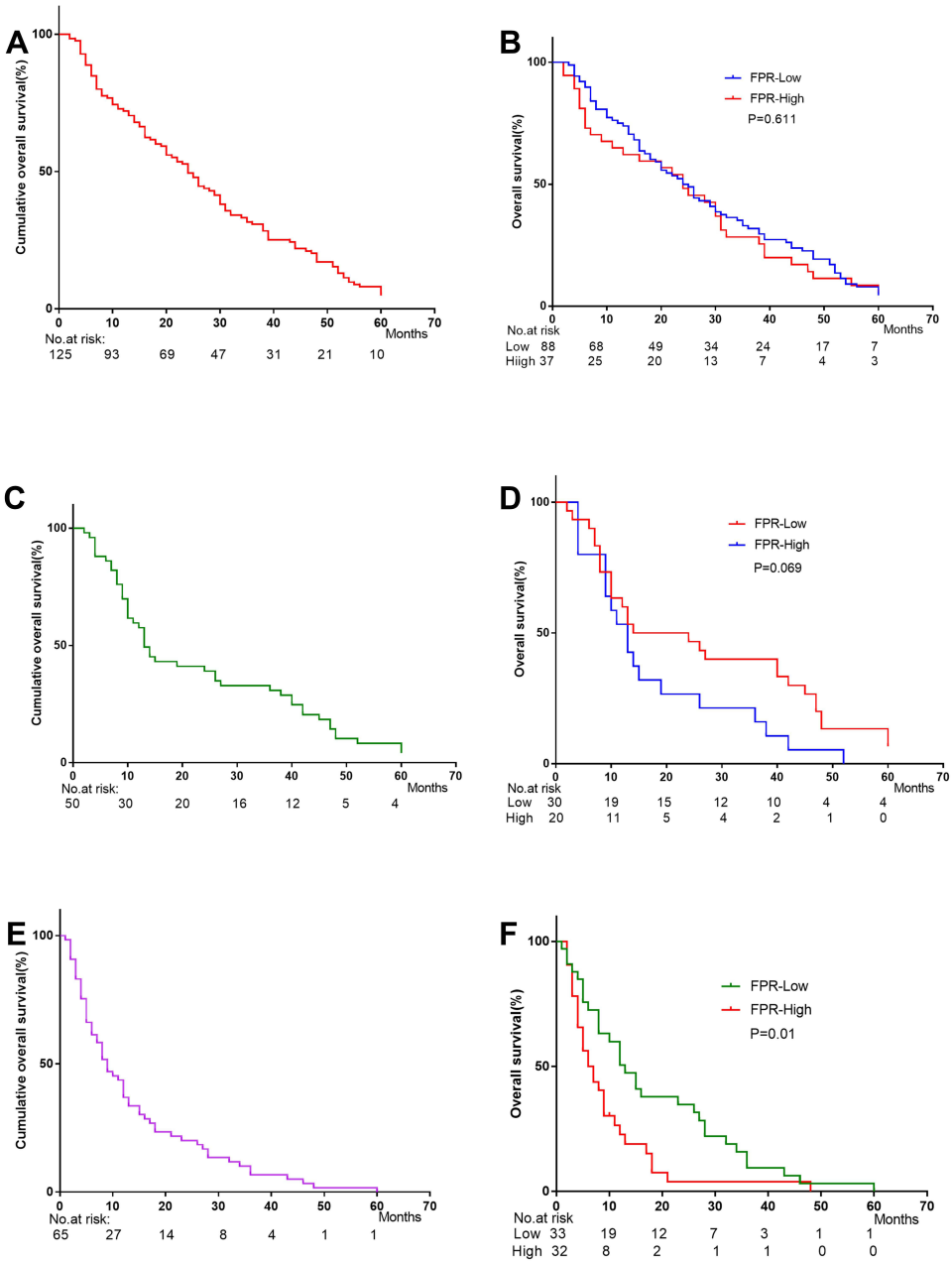

Figure 3 Stratified cumulative overall survival curve and Kaplan–Meier curves analysis on FPR according to BCLC stage.
Notes: (**A**) Cumulative overall survival curve in BCLC A; (**B**) 5-year OS of FPR in BCLC A; (**C**) Cumulative overall survival curve in BCLC B; (**D**) 5-year OS of FPR in BCLC B; (**E**) Cumulative overall survival curve in BCLC C; (**F**) 5-year OS of FPR in BCLC C.
Abbreviation: FPR, fibrinogen/prealbumin ratio.

lower FPR; however, statistically significant difference was not observed. The cumulative overall survival at 10, 20, 30, 40, 50, and 60 months was 74.4%, 55.2%, 37.6%, 24.8%, 16.8%, 8%, and 60%, 40%, 32%, 24%, 10%, 8%, respectively (Figure 3A, Figure 3C).

Prognostic Value of FPR for 5-Year OS

In this study, Cox proportion regression model was used to investigate the prognostic effects of the basic characteristics and FPR, PLR, LMR, NLR, and PNI in HCC. According to the univariate analysis, the tumor diameter (P = 0.001),

Table 6 Overall Survival Analysis

Variable	Univariate	P	Multivariate	P
	HR (95% CI)		HR (95% CI)	
Sex (male/female)	0.980 (0.908–1.058)	0.607		
Age (<60/≥60)	1.001 (0.998–1.003)	0.784		
Tumor diameter (cm) (≤5/>5)	1.035 (1.026–1.044)	0.001	1.035 (1.025–1.046)	0.000
Tumor number (1/≥2)	0.976 (0.946–1.007)	0.124		
Vascular invasion (No/Yes)	1.110 (1.033–1.193)	0.004	1.190 (1.100–1.287)	0.000
AFP (ng/mL)(≤400/>400)	1.002 (1.001–1.004)	0.000	1.002 (1.001–1.005)	0.000
Cirrhosis (No/Yes)	1.189 (1.100–1.285)	0.000	1.162 (1.068–1.265)	0.000
Child-Pugh grade (A/B)	0.990 (0.932–1.052)	0.749		
CEA	1.003 (0.997,1.010)	0.304		
PNI	1.001 (0.990–1.009)	0.533		
NLR	1.046 (1.033–1.059)	0.000	1.043 (1.028–1.097)	0.000
LMR	1.043 (1.026–1.060)	0.000	1.079 (1.061–1.097)	0.000
PLR	1.002 (1.001–1.009)	0.001	1.002 (1.001–1.004)	0.033
FPR	1.010 (1.007–1.014)	0.000	1.009 (1.006–1.013)	0.000

Abbreviations: AFP, alpha-fetoprotein; CEA, carcinoembryonic antigen; FPR, fibrinogen/prealbumin ratio; PNI, albumin (g/L)+ 5× lymphocyte (109 /L); PLR, platelet/lymphocyte ratio; NLR, neutrophil/lymphocyte ratio; LMR, lymphocyte/monocyte ratio.

vascular invasion (P = 0.004), AFP (P = 0.000), cirrhosis (P = 0.000), NLR (P = 0.000), LMR (P = 0.000), PLR (P = 0.00), and FPR (P = 0.000) were all associated with 5-year OS (Table 6).

Besides, multivariate logistic regression analysis showed that FPR (95% confidence interval: 1.006–1.013, hazard ratio: 1.009) was a prognostic factor for the prediction of 5-year OS in HCC. Moreover, the size of the tumor, vascular invasion, AFP, cirrhosis, NLR, LMR, and PLR also showed prognostic value in predicting 5-year OS (Table 6).

Moreover, a nomogram was established for predicting OS, and 8 significant variables proved by multivariate analysis were used (Figure 4A). C-index was 0.604 (95% CI: 0.521–0.756) as shown by the model (Figure 4B).

Discussion

HCC diagnosis at an early stage is highly related to the prognosis and could increase the 5-year survival rate.[12] Nowadays, BCLC stage and cell differentiation classification are the most effective and important prognostic indicators

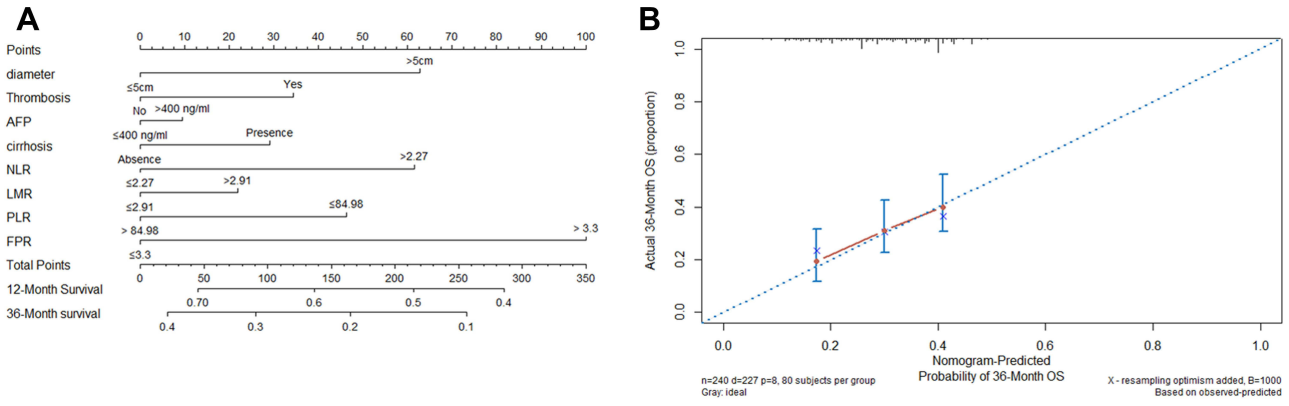

Figure 4 Nomography to predict OS of HCC patients.
Notes: (**A**) Prognostic nomogram with FPR. (**B**) The calibration curves.
Abbreviations: AFP, alpha-fetoprotein; FPR, fibrinogen/prealbumin ratio; PLR, platelet/lymphocyte ratio; NLR, neutrophil/lymphocyte ratio; LMR, lymphocyte/monocyte ratio.

for this disease. AFP, which regulates and monitors HCC, still has limitations in detecting HCC, with unsatisfactory diagnostic function.[13] Therefore, it is urgent to discover new and useful markers to evaluate HCC development.

It was demonstrated that HCC development could be influenced by nutritional status and coagulation. Fibrinogen, a kind of reacting glycoprotein in the acute phase, is mainly generated in hepatocytes.[14] A research by Zhu et al[15] presented that mRNA expression of fibrinogen was upregulated in vivo and in vitro, and the elevated fibrinogen level in plasma was related to thrombosis in tumor. Additionally, it was suggested that an elevated fibrinogen level in plasma was associated with the prognosis of ovarian cancer.[16,17] Thus, the FPR level might be increased in malignancies.

A high level of FPR before operation was remarkably related to a larger size of tumor and a more advanced HCC stage, indicating that FPR could indicate HCC phenotype. These results were consistent with previous research on HCC, CRC, and GC.[18–20] Wang et al[21] demonstrated that the ratio of prealbumin/fibrinogen was decreased in critical acute pancreatitis and negatively correlated with its development. Furthermore, a high level of FPR in circulating blood was remarkably related to worse OS of patients with HCC after treatment of TACE and RFA, implying that FPR could be independently used as a factor predicting the prognosis. Certain research also presented that FPR before operation could be used in predicting the prognosis of multiple solid tumors.[16,22]

The mechanisms underlying the relationship between FPR and HCC are still unclear. Some hypothesis may explain our results. Firstly, fibrinogen might influence the biological activities and function of cancer cells.[23] The connection between VEGF, PGF, TGF-B and Fib could result in proliferation, metastasis, and angiogenesis of cancer cells and suppress cellular apoptosis.[24] Secondly, platelet-fibrin microthrombi provided a barrier to separate tumor cells and natural killer cells to prevent their contact and enhance metastasis.[25] Fib also provided a bridge between normal cells and tumor cells, and increased the adhesion between cancer cell emboli in the vessels.[26] Thirdly, pAlb in circulating blood could indicate nutrition status and chronic inflammation in the patients with malignancy. Lack of nutrition is a common disorder in cancer,[27] and nutritional status remarkably influenced the tolerance to chemotherapy and survival.[28]

However, there are some limitations in this study. Firstly, the study was retrospective in nature, and the sample size was relatively small, which might result in unavoidable bias. Secondly, there might be bias in the evaluation of the predictive effects of the markers since it was a single-center study. Thus, our findings remain to be further verified by prospective, multiple-center and large-scale studies.

Conclusion

Our research indicated that FPR was a potential indicator for patients with BCLC A-C hepatocellular carcinoma after treatment of RFA and TACE.

Acknowledgment

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Disclosure

The authors declare no conflicts of interest in this work.

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