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 fetoprotein (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.5,9 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.
Table 1 Clinical and Pathological Features

| Variables                | No. of Patients |
|--------------------------|-----------------|
| Male/female              | 200/40          |
| Age (years)              | 59(52.68)       |
| Tumor diameter (cm)      | 4(2.9,6.66)     |
| 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-tile 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.
In this study, 240 patients at stage BCLC-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.

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

| Variable                        | FPR            | \( \chi^2 / t \) | P     |
|---------------------------------|----------------|-----------------|-------|
|                                 | Low (n=151)    |                 |       |
|                                 | High (n=89)    |                 |       |
| Sex                             |                |                 |       |
| Male                            | 124            |                 |       |
| Female                          | 27             |                 |       |
| 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               |                |                 |       |
| No                              | 120            | 62              |       |
| Yes                             | 31             | 27              |       |
| AFP (ng/mL)                     |                |                 |       |
| ≤400                            | 117            | 71              | 0.173 | 0.677 |
| >400                            | 34             | 18              |       |
| Cirrhosis                       |                |                 |       |
| No                              | 25             | 15              | 0.004 | 0.952 |
| Yes                             | 126            | 74              |       |
| Child-Pugh grade                |                |                 |       |
| A                               | 108            | 45              | 10.647| 0.001 |
| 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.
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 (10⁹ /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). 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.

Table 3 Correlation Between Clinical Characteristics and FPR in BCLC a

| Variable                   | Case (125) | FPR           | χ²/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   | 3.5  | 0.061|
| CEA                        | 4.13±2.87  | 4.17±2.98     | 0.056| 0.814|
| NLR                        | 4.29±3.02  | 2.74±1.31     | 0.1   | 0.919|
| PLR                        | 106.04±48.38| 112.86±73.82 | 0.136| 0.245|
| LMR                        | 3.36±1.82  | 3.56±1.90     | 0.041| 0.839|
| PNI                        | 41.14±7.83 | 42.63±8.08    | 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 (10⁹ /L).
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 | χ²/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  | χ²/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              | I         | 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
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 ($P = 0.001$),
vascular invasion (P = 0.004), AFP (P = 0.000), cirrhosis (P = 0.000), NLR (P = 0.000), LMR (P = 0.000), 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.
for this disease. AFP, which regulates and monitors HCC, still has limitations in detecting HCC, with unsatisfactory diagnostic function. 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. A research by Zhu et al 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. 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. Wang et al 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.

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. The connection between VEGF, PGF, TGF-B and Fib could result in proliferation, metastasis, and angiogenesis of cancer cells and suppress cellular apoptosis. Secondly, platelet-fibrin microthrombi provided a barrier to separate tumor cells and natural killer cells to prevent their contact and enhance metastasis. Fib also provided a bridge between normal cells and tumor cells, and increased the adhesion between cancer cell emboli in the vessels. 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, and nutritional status remarkably influenced the tolerance to chemotherapy and survival.

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**

The current research was funded by Capital Health development Scientific Research project (Shou fa 2022-2-2175).

**Disclosure**

The authors declare no conflicts of interest in this work.

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