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ORIGINAL ARTICLE

Differential Expression and Diagnostic Significance of Pre-Albumin, Fibrinogen Combined with D-Dimer in AFP-Negative Hepatocellular Carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is one of the most malignant cancers with high morbidity and mortality. Nowadays, AFP-negative hepatocellular carcinoma (AFP-NHCC) has been found in many HCC patients and AFP analysis can't be used to screen HCC in these cases. In this study, we have examined the expression patterns of pre-albumin (PA), fibrinogen, D-Dimer and their clinical significance in AFP-NHCC. We recruited 214 AFP-NHCC patients and 210 controls in the study. PA, fibrinogen and D-Dimer levels were detected by turbidimetry, clauss and immunoturbidimetry methods, respectively. Serum PA levels were significantly lower in AFP-NHCC (84.5 ± 24.7 mg/L) than that in the controls (240.6 ± 59.4 mg/L, $P < 0.05$). For plasma fibrinogen levels, there was no difference between the controls (2.9 ± 0.7 g/L) and AFP-NHCC (2.5 ± 0.7 g/L). Compared with AFP-NHCC (0.8 ± 0.2 mg/L), plasma D-Dimer levels were significantly lower in controls (0.1 ± 0.0 mg/L, $P < 0.05$). The levels of PA, fibrinogen and D-Dimer were significantly correlated with differentiation ($P < 0.01$), and the PA and D-Dimer values were correlated with TNM stage ($P < 0.05$). Moreover, PA levels were correlated with tumor size ($P = 0.034$). Receiver operating characteristic curve (ROC) analyses elaborated that combination of PA, fibrinogen and D-Dimer possessed a higher sensitivity (93.4%) for differentiating AFP-NHCC from the controls, but the diagnostic specificity was reduced due to the combination of fibrinogen. After adjusting for all significant outcome predictors of the univariate logistic regression analysis, low levels of PA and high levels of D-Dimer were remained independent unfavorable outcome predictors ($P < 0.05$). Our data suggested that the expression levels of PA, fibrinogen and D-Dimer played critical roles in AFP-NHCC tumorigenesis. Moreover, PA and D-Dimer might be considered as potential diagnostic indicators in AFP-NHCC.

Keywords Pre-albumin · Fibrinogen · D-Dimer · AFP-negative hepatocellular carcinoma · Diagnosis

Introduction

Liver cancer is one of the most common malignant tumors, which is also the common death-related diseases in China. Among primary liver cancers, 85%–90% are hepatocellular carcinoma (HCC) [1]. Cirrhosis is recognized as the most important risk factor for HCC formation, with an incidence of 80%–90% [2]. Over the past 10 years, HCC mortality has increased significantly, and epidemiological studies have shown that the drug and economic burden of HCC will continue to increase significantly.

For decades, HCC screening relied primarily on ultrasound imaging and alpha-fetoprotein (AFP). Due to technical limitations, ultrasound images are often unrecognizable for HCC

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nodules less than 1 cm [3]. AFP is the most important and traditional serological diagnostic indicator for HCC, but AFP is measured separately in early HCC with a missed diagnosis rate of 40% [4]. Even though 15%–30% of serum AFP is at a normal level (<20 ng/mL) in advanced patients, we refer to this type of HCC as AFP-negative hepatocellular carcinoma (AFP-NHCC) [4]. AFP-NHCC accounts for about 30%–40% of HCC, and is an important type of liver cancer that currently causes many HCC patients to lose early diagnosis and treatment, especially in HCC with tumors less than 3 cm [4]. The clinical symptoms of AFP-NHCC patients are usually mild and lack specificity, and their clinical diagnosis rely mainly on imaging and other tumor marker tests. However, because the tumor of AFP-NHCC is usually small, imaging examination is prone to missed diagnosis. It is reported that the diagnostic rates of AFP-NHCC patients by CT, MRI and B-ultrasound are about 50.9%, 50.0%, 10.4%, respectively [5]. In addition, liver nodular lesions such as cirrhosis regenerative nodules, hepatic focal nodular hyperplasia, hepatic adenomas, etc. may also have HCC-like imaging findings, making AFP-NHCC patients easily misdiagnosed as benign disease, and lose the opportunity for early treatment.

Pre-albumin (PA) is synthesized by hepatocytes. Its concentration in serum is sensitive to protein malnutrition, liver dysfunction, and is more sensitive than albumin and transferrin [6]. In addition to being a sensitive nutrient protein indicator, PA concentrations are also reduced in malignancies. Wen et al. [7] found that the preoperative serum PA was a valuable prognosis predicting biomarker for HCC patients who may be under consideration for curative resection, and lower level of pre-surgery PA was an independent factor of poor post-surgery prognosis in HCC patients. Fibrinogen and D-Dimer are two important indicators of the blood coagulation state of the reaction body. In the process of malignant tumors, due to the infiltration, metastasis, and destruction of tumor cells, a large amount of pro-coagulant substances are allowed to enter the blood, causing the body to be in a hypercoagulable state [8–10]. Up to now, the expression characteristic and diagnostic values of PA, fibrinogen and D-Dimer in AFP-NHCC have not been reported.

In this study, we examined the expression levels of PA, fibrinogen and D-Dimer in 214 AFP-NHCC patients and 210 controls, aiming to provide new ideas for the differential diagnosis of AFP-NHCC.

Materials and Methods

Experimental Subjects

We recruited 214 patients (168 men and 46 women; median age: 53, interquartile range [IQR]: 44–67) who were diagnosed as AFP-NHCC in the First Affiliated Hospital of Zhengzhou University. The diagnosis of AFP-NHCC was confirmed by liver puncture or surgical histopathology examination. At the same time, we also collected 210 age and gender matched controls, including 162 males and 48 females, median age: 53, interquartile range [IQR]: 45–67. All the controls were without hepatitis, hepatic diseases, abnormal liver biochemical outcome, inflammation, thrombosis or malnutrition.

Ethical Approval and Consent to Participate

This study was all approved by the Ethics Committee of The First Affiliated Hospital of Zhengzhou University. Written informed consent was provided in accordance with the Declaration of Helsinki.

Clinical Data Collection

Clinical information was collected, including the following: gender, age, smoking history and drinking history. Laboratory information, such as serum liver function indicators including alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL) and γ-glutamyl transpeptidase (GGT), was also gathered.

Sample Collection and PA, Fibrinogen and D-Dimer Testing

Sodium citrate (1: 9) collection tube was used to collect 3 mL of venous blood. After centrifugation at 3500 g (centrifugation radius was 10 cm) for 5 min at 15 °C -18 °C, the upper plasma was collected for detection of fibrinogen and D-Dimer levels. The levels of fibrinogen were determined using the clauss method. D-Dimer levels were determined using the immunoturbidimetry method. In all samples, fibrinogen and D-dimer were assayed using the ACL TOP system (Instrumentation Laboratory, Milan, Italy). For the analysis of PA, blood was drawn in vacuum tube filled with separation gel and centrifuged at 3500 rpm for 5 min, and then PA was analyzed by cobas 8000 automatic biochemistry analyzer (Roche Diagnostics, Indianapolis, USA). PA levels were determined using the turbidimetry method. The quality of laboratory data was validated throughout the study period by regular internal quality control procedures and participation in an External Quality Assessment Scheme.

Statistical Analysis

Statistical analysis was performed using SPSS 22.0. Normal distribution data was presented as mean ± standard deviation (M ± SD). Non-normally distributed data was expressed in quartiles. For normally distributed data, differences between two groups were evaluated by Student's t test. For non-normally distributed variables, Mann-Whitney U-test was

Table 1 Comparison of baseline characteristics between AFP-NHCC and controls

Characteristics	AFP-NHCC $N=214$	Controls $N=210$	P
Age (years), median (IQR)	53 (44, 67)	53 (45, 67)	0.693 [b]
Male sex (n), %	168 (78.50%)	162 (77.14%)	0.736 [a]
Smoking (n), %	128 (59.81%)	121 (57.62%)	0.646 [a]
Drinking (n), %	145 (67.76%)	134 (63.81%)	0.392 [a]
TBIL (μmol/L), median (IQR)	27.13 (15.63, 62.27) [c]	17.42 (12.26, 19.67)	<0.001 [b]
ALT (U/L), median (IQR)	48.45 (27.12, 98.73) [c]	16.68 (14.18, 22.83)	<0.001 [b]
AST (U/L), median (IQR)	72.75 (31.34, 118.42) [c]	21.97 (18.33, 27.87)	<0.001 [b]
GGT (U/L), median (IQR)	64.24 (28.30, 127.93) [c]	16.56 (13.65, 24.53)	<0.001 [b]

[a] Chi-square test. [b] Mann-Whitney U-test. [c] Compared with controls, $P<0.05$. ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; GGT, γ-glutamyl transpeptidase

used to evaluate the difference between two groups. The categorical variables were analyzed using Chi-square test. Receiver operating characteristic curve (ROC) analysis was performed to estimate the value of PA, fibrinogen and D-Dimer to discriminate AFP-NHCC, and the area under the curve (AUC), the 95% confidence interval (CI), and the corresponding diagnostic sensitivity, specificity, positive and negative predictive values were also calculated. Binary logistic regression analysis was used to calculate the odds ratio (OR) and 95% CI for PA, fibrinogen and D-Dimer, and the covariates included gender, age, smoking history, drinking history, ALT, AST, TBIL, and GGT. In this study, $P<0.05$ was considered to be statistically significant.

Results

Study Characteristics

The main baseline characteristics of the studied subjects were illustrated in Table 1. No significant differences were observed in age, sex ratio, smoking history and drinking history between the two groups ($P>0.05$). There was a significant difference in ALT, AST, TBIL and GGT ($P<0.05$).

Comparison of PA, Fibrinogen and D-Dimer Levels in AFP-NHCC and Controls

The reference ranges of PA, fibrinogen and D-Dimer were as follows: 180–400 mg/L for PA, 2.0–4.0 g/L for fibrinogen and 0.0–0.3 mg/L for D-Dimer. Our results demonstrated that serum PA levels were significantly lower in AFP-NHCC (84.5 ± 24.7 mg/L) than that in the controls (240.6 ± 59.4 mg/L, $P<0.05$) (Fig. 1a). For plasma fibrinogen levels, there was no difference between the AFP-NHCC (2.5 ± 0.7 g/L) and controls (2.9 ± 0.7 g/L) (Fig. 1b). Compared with AFP-NHCC (0.8 ± 0.2 mg/L), plasma D-Dimer levels were significantly lower in the controls (0.1 ± 0.0 mg/L, $P<0.05$) (Fig. 1c).

Correlation between PA, Fibrinogen, D-Dimer Levels and Clinical Parameters of AFP-NHCC

As shown in Table 2, the levels of PA and D-Dimer were significantly correlated with differentiation ($P<0.01$) and TNM stage ($P<0.05$), and the levels of PA were significantly correlated with tumor size ($P=0.034$). Meanwhile, there was a relationship between fibrinogen levels and differentiation ($P<0.01$). No statistically significant relevancies were found in age, gender, smoking history, drinking history and cirrhosis ($P>0.05$).

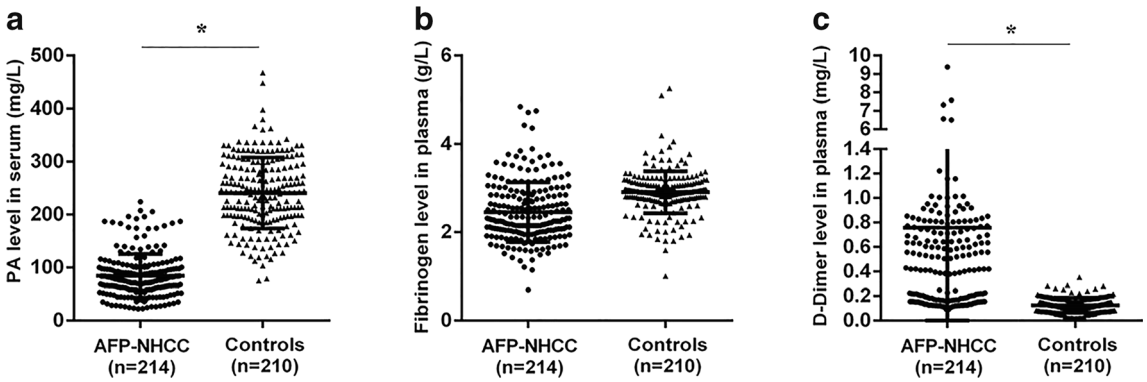

Fig. 1 PA, Fibrinogen and D-Dimer levels in AFP-NHCC and controls. **a** PA level in serum. **b** Fibrinogen level in plasma. **c** D-Dimer level in plasma. * $P<0.05$

Table 2 Relationship between PA, fibrinogen and D-Dimer and clinical features of AFP-NHCC

Characteristics	N	PA (mg/L)			Fibrinogen (g/L)			D-Dimer (mg/L)		
		M ± SD	*t*	*P*	M ± SD	*t*	*P*	M ± SD	*t*	*P*
Differentiation			7.132	**<0.001**		−12.476	**<0.001**		−4.516	**<0.001**
High	55	109.7 ± 23.7			2.0 ± 0.8			0.6 ± 0.2		
Moderate/low	159	75.8 ± 18.0			2.7 ± 1.1			0.9 ± 0.3		
Tumor size (cm)			2.129	**0.034**		−1.887	0.091		1.817	0.101
<3	143	88.8 ± 24.0			2.4 ± 0.7			0.8 ± 0.2		
≥3	71	81.8 ± 19.6			2.7 ± 0.8			0.7 ± 0.1		
TNM stage			10.146	**<0.001**		−1.176	0.241		−2.514	**0.012**
I-II	69	110.2 ± 27.1			2.5 ± 0.8			0.6 ± 0.2		
III-IV	145	72.3 ± 21.4			2.7 ± 1.3			0.7 ± 0.3		

The bold represents the meaningful data

Diagnostic Value Analysis

To estimate the diagnostic value of PA, fibrinogen and D-Dimer between AFP-NHCC and controls, ROC was constructed (Fig. 2, Table 3). The AUC_{ROC} indicated that PA and D-Dimer levels possessed a moderate ability for detecting AFP-NHCC patients from controls, respectively (AUC = 0.900, 0.868). However, the diagnostic value of fibrinogen was not noticeable in discriminating AFP-NHCC patients and controls. Moreover, combination of PA and D-Dimer levels possessed a good specificity of 89.2% in identifying AFP-NHCC patients from controls. When we combined the three indicators for differentiating AFP-NHCC from controls, we found that the diagnostic sensitivity raised up to 93.4%, but the specificity decreased. Therefore, combination of circulating PA, fibrinogen and D-Dimer levels might serve as combined diagnostic indicators for early diagnosis of AFP-NHCC, but the diagnostic specificity was reduced by the combination of fibrinogen.

Univariate and Multivariate Logistic Regression Analyses for AFP-NHCC

In univariate logistic regression analysis, PA, fibrinogen and D-Dimer levels compared with other risk factors are presented in Table 4. After adjusting for all significant outcome predictors of the univariate logistic regression analysis, low levels of PA and high levels of D-Dimer were remained independent unfavorable outcome predictors ($P < 0.05$).

Discussion

Although there are great developments in the current treatment of HCC, including surgical resection, liver transplantation, adjuvant therapy and interventional therapy. Many HCC patients are diagnosed after the occurrence of relevant clinical symptoms, and most of them are in advanced stage, resulting in a low 5-year survival rate [11, 12]. It is worth noting that the

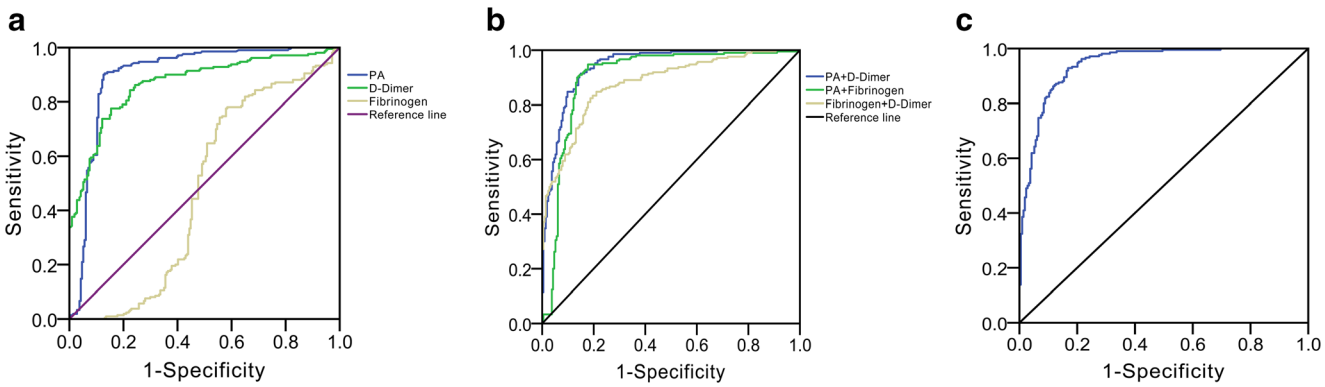

Fig. 2 Receiver operating characteristic curves. **a** Differential diagnosis value of single index for AFP-NHCC. **b** Differential diagnosis value of two indicators for AFP-NHCC. **c** Differential diagnosis value of three indicators for AFP-NHCC

Table 3 ROC analysis of PA, fibrinogen and D-Dimer values between AFP-NHCC and controls

Group	AUC	95% CI	*P*	Se (%)	Sp (%)	PPV	NPV
PA	0.900	0.867–0.934	<0.001	90.1%	86.3%	87.0%	89.5%
Fibrinogen	0.476	0.418–0.534	0.393	70.6%	40.1%	54.5%	57.2%
D-Dimer	0.868	0.833–0.903	<0.001	73.8%	87.1%	85.4%	76.5%
PA + D-Dimer	0.941	0.920–0.963	<0.001	85.7%	89.2%	89.0%	86.0%
PA + Fibrinogen	0.904	0.871–0.937	<0.001	89.8%	83.6%	84.8%	88.9%
D-Dimer+Fibrinogen	0.879	0.847–0.911	<0.001	82.4%	79.8%	80.6%	81.6%
PA + D-Dimer+Fibrinogen	0.943	0.921–0.964	<0.001	93.4%	80.8%	83.2%	92.3%

AUC, area under the receiver operating characteristic curves; *CI*, confidence interval; *Se*, sensitivity; *Sp*, specificity; *PPV*, positive predictive value; *NPV*, negative predictive value

5-year survival rate of HCC patients who were diagnosed early and treated with appropriate treatment exceeded 50%, suggesting that early screening can effectively reduce HCC mortality [13].

PA, also called transthyretin, is an acute phase response protein with a half-life of only 2.5 days that can reflect liver synthesis and reserve function [14]. Hepatocyte damage or inflammatory stimulation can alter PA levels. Studies have shown that the level of PA is more sensitive than other indicators in liver disease, and PA level is reduced in approximately 30% of patients with normal albumin [15]. PA is also used as a predictor of nutritional status, morbidity and mortality [16]. Nutritional status closely correlates with tumor progression. Several studies have suggested that PA levels may be related to liver function and therefore show prognostic value. Jia et al. [17] collected and followed up 526 patients with HCC and found that the 10-year survival rate of patients with low PA level (<182 mg/L) was significantly lower than that with high PA level (>182 mg/L). They also found that low PA level (<182 mg/L) was related to tumor size and macrovascular invasion. However, the expression characteristic of PA in AFP-NHCC has not been reported. In the present study, for the first time, we investigated the clinical value of PA in AFP-NHCC patients. We found that serum PA levels were significantly lower in AFP-NHCC than in controls. Meanwhile, correlation analysis results showed that PA levels were related to differentiation, tumor size and TNM stage. The area under the ROC elaborated that the value of PA was helpful for differentiating AFP-NHCC patients from the controls, with good sensitivity (90.1%) and specificity (86.3%). Our current findings suggest that PA reduction is also well correlated with malignant biological processes in APF-NHCC patients and can be used for clinical diagnosis and evaluation of patients with AFP-NHCC.

Plasma fibrinogen is synthesized by liver and is an acute-phase soluble glycoprotein [18]. Fibrinogen is a 350-kDa glycoprotein that comprises 2 sets of 3 different polypeptide chains, a, b, and c, and plays a major role in hemostasis,

Table 4 Logistic regression analyses for AFP-NHCC

Parameter	Univariate analysis		Multivariate analysis [b]	
	OR (95% CI)[a]	*P*	OR (95% CI)[a]	*P*
Age	1.039 (0.982, 1.138)	0.904		
Male sex	1.030 (0.576, 1.782)	0.681		
Smoking	0.896 (0.987, 1.237)	0.204		
Drinking	1.085 (0.916, 1.536)	0.172		
TBIL	0.995 (0.882, 1.446)	0.826		
ALT	1.051 (0.557, 1.984)	0.878		
AST	1.786 (0.906, 3.522)	0.094		
GGT	1.242 (0.643, 2.398)	0.519		
PA	0.764 (0.593, 0.906)	<0.001	0.804 (0.616, 0.927)	<0.001
Fibrinogen	1.060 (0.989, 1.103)	0.134		
D-Dimer	1.198 (1.067, 1.311)	<0.001	1.215 (1.074, 1.335)	<0.001

OR, odds ratio; *CI*, confidence interval; *ALT*, alanine aminotransferase; *AST*, aspartate aminotransferase; *TBIL*, total bilirubin; *GGT*, γ-glutamyl transpeptidase; *PA*, Pre-albumin

[a] Note that the odds ratio corresponds to a unit increase in the explanatory variable; [b] OR was adjusted for all significant outcome predictors of the univariate logistic regression analysis

thrombosis and platelet aggregation [19]. Fibrinogen is widely known for its association with the maintenance of hemostatic function, but recent substantial evidence indicates that plasma fibrinogen levels also play critical roles in patients with HCC and are closely associated with metastasis, disease progression, and poor prognosis [20, 21]. The expression and clinical value of fibrinogen in AFP-NHCC has not been reported. In our research, the levels of plasma fibrinogen were no difference between the AFP-NHCC and controls. Meanwhile, fibrinogen was unhelpful to diagnose between AFP-NHCC and controls. However, we found that there was a relationship between plasma fibrinogen levels and differentiation. The plasma fibrinogen levels were significantly higher in the moderately/poorly differentiated patients than that in the well differentiated cases. The possible mechanisms accounting for the link between high plasma fibrinogen and tumor differentiation are as follows. Firstly, high plasma fibrinogen may be associated with increased fibrinogen deposits in tumor tissue. In the process of malignant tumors, due to the infiltration, metastasis and destruction of tumor cells, a large amount of pro-coagulant substances are injected into the blood, and the cells release secretory mucin, tissue factor, then destroy vascular endothelial cells, inhibit thrombin expression, and promote blood coagulation activity, thereby raising the level of fibrinogen, causing the body to be in a hypercoagulable state [22]. Secondly, in the case of malignant tumors, the fibrinogen concentration is increased, which can enhance the adhesion of platelets to cancer cells, thereby facilitating the metastasis of cancer cells [23]. Lastly, chronic inflammatory responses play critical roles in tumor development and progression. In particular, there is a close relationship between fibrinogen and systemic inflammation [24]. However, studies with more cases need to be further researched.

D-Dimer is a degradation product of the cross-linked fibrin polymer that is degraded by plasmin during fibrinolysis [25]. Previous studies have reported that plasma D-Dimer levels can predict poor prognosis in several types of malignancies, including ovarian [26], breast [27], colorectal [28] and lung cancer [29]. This study we found that plasma D-Dimer levels in AFP-NHCC were significantly higher than that in controls. In addition, we also found that D-Dimer values were significantly correlated with differentiation and TNM stage. Most importantly, D-Dimer levels yielded an AUC of 0.868 (73.8% sensitivity, 87.1% specificity) for differentiating AFP-NHCC from controls. Many studies have pointed out that due to the invasion of tumor cells and the damage of tumor cells to the vascular endothelium, tumor patients are accompanied by different degrees of coagulation abnormalities [30]. Studies have also shown that due to the tumor wrapped in the network structure, as the disease develops or the rate of metastasis accelerates, the network structure is destroyed, then the release of D-Dimer is increased, and thrombotic diseases are easily prone to occur [31]. However, the exact explanation needs further research.

For the first time, we assessed the expression levels of PA, fibrinogen and D-Dimer to analysis the clinical value in AFP-NHCC. The AUC elaborated that combination of PA, fibrinogen and D-Dimer possessed a higher sensitivity for differentiating AFP-NHCC from controls, but the specificity was reduced by the combination of fibrinogen. Our results suggested that the levels of PA and D-Dimer were meaningful markers in detecting AFP-NHCC from the controls. In multivariate logistic regression analyses, after adjusting for all significant outcome predictors of the univariate logistic regression analysis, low levels of PA and high levels of D-Dimer were remained independent unfavorable outcome predictors. However, the number of AFP-NHCC cases included in this study is limited. A multi-center cohort study is needed in the future to further validate the results of the study, and a large sample of study is needed to confirm the clinical values of PA, fibrinogen and D-Dimer in AFP-NHCC patients in China.

Conclusion

In our research, results showed that the expression levels of PA, fibrinogen and D-Dimer played important roles in AFP-NHCC tumorigenesis. Moreover, PA and D-Dimer might be served as potential diagnostic indicators in AFP-NHCC.

Compliance with Ethical Standards

Competing Interests The authors have declared that no conflict of interest.

References

1. Corwin MT, Lee AY, Fananapazir G, Loehfelm TW, Sarkar S, Sirlin CB (2018) Nonstandardized terminology to describe focal liver lesions in patients at risk for hepatocellular carcinoma: implications regarding clinical communication. AJR Am J Roentgenol 210(1): 85–90. https://doi.org/10.2214/ajr.17.18416
2. Nadinskaia MY, Kodzoeva KB, Ulyanova KA, Volkova AS, Rogacheva SI, Dekhanov AS, Strelkova DA, Ivashkin VT (2019) Risk factors associated with portal vein thrombosis in liver cirrhosis: a case-control study. Terapevticheskii arkhiv 91(2):73–81. https://doi.org/10.26442/00403660.2019.02.000153
3. Monfardini L, Orsi F, Caserta R, Sallemi C, Della Vigna P, Bonomo G, Varano G, Solbiati L, Mauri G (2018) Ultrasound and cone beam CT fusion for liver ablation: technical note. International journal of hyperthermia : the official journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group. 35(1):500–504. https://doi.org/10.1080/02656736.2018.1509237

4. Wang M, Devarajan K, Singal AG, Marrero JA, Dai J, Feng Z, Rinaudo JA, Srivastava S, Evans A, Hann HW, Lai Y, Yang H, Block TM, Mehta A (2016) The Doylestown algorithm: a test to improve the performance of AFP in the detection of hepatocellular carcinoma. Cancer Prev Res (Phila) 9(2):172–179. https://doi.org/10.1158/1940-6207.capr-15-0186
5. Chen ZZ, Huang L, Wu YH, Zhai WJ, Zhu PP, Gao YF (2016) LncSox4 promotes the self-renewal of liver tumour-initiating cells through Stat3-mediated Sox4 expression. Nat Commun 7:12598. https://doi.org/10.1038/ncomms12598
6. Arbab K, Majid H, Jafri L, Akram B, Raheem A, Jamil B, Hashmi M, Khan AH (2019) Assessing nutritional status of critically ill patients using serum Prealbumin levels. J Ayub Med Coll, Abbottabad : JAMC 31(2):178–181
7. Wen X, Yao M, Lu Y, Chen J, Zhou J, Chen X, Zhang Y, Lu W, Qian X, Zhao J, Zhang L, Ding S, Lu F (2018) Integration of Prealbumin into child-Pugh classification improves prognosis predicting accuracy in HCC patients considering curative surgery. J Clin Transl Hepatol 6(4):377–384. https://doi.org/10.14218/jcth.2018.00004
8. Hou C, Jiang F, Ma H, Zhu Q, Wang Z, Zhao B, Xue T, Tan S, Yang R, Qian Y, Luo X, Zhao M, Xu X, Chen L, Li J (2019) Prognostic role of preoperative platelet, fibrinogen, and D-dimer levels in patients with non-small cell lung cancer: a multicenter prospective study. Thoracic Cancer 10(2):304–311. https://doi.org/10.1111/1759-7714.12956
9. Cai HX, Li XQ, Wang SF (2018) Prognostic value of fibrinogen and D-dimer-fibrinogen ratio in resectable gastrointestinal stromal tumors. World J Gastroenterol 24(44):5046–5056. https://doi.org/10.3748/wjg.v24.i44.5046
10. Fan S, Zhao G, An G (2019) High pretreatment plasma D-dimer levels are associated with shorter overall survival in patients with small cell lung cancer. J Int Med Res 47(1):215–224. https://doi.org/10.1177/0300060518799869
11. Darweesh SK, Gad AA (2019) Percutaneous microwave ablation for HCV-related hepatocellular carcinoma: efficacy, safety, and survival. Turk J Gastroenterol 30(5):445–453. https://doi.org/10.5152/tjg.2019.17191
12. Yamada R, Bassaco B, Bracewell S, Gillen K, Kocher M, Collins H, Anderson MB, Guimaraes M (2019) Long-term follow-up after conventional transarterial chemoembolization (c-TACE) with mitomycin for hepatocellular carcinoma (HCC). J Gastrointest Oncol 10(2):348–353. https://doi.org/10.21037/jgo.2019.01.01
13. Fung J, Cheung KS, Wong DK, Mak LY, To WP, Seto WK, Lai CL, Yuen MF (2018) Long-term outcomes and predictive scores for hepatocellular carcinoma and hepatitis B surface antigen seroclearance after hepatitis B e-antigen seroclearance. Hepatology (Baltimore, Md) 68(2):462–472. https://doi.org/10.1002/hep.29874
14. Fan L, Chi C, Guo S, Wang Y, Cai W, Shao X, Xu F, Pan J, Zhu Y, Shangguan X, Xin Z, Hu J, Qian H, Xie S, Wang R, Zhou L, Dong B, Xue W (2017) Serum pre-albumin predicts the clinical outcome in metastatic castration-resistant prostate Cancer patients treated with Abiraterone. J Cancer 8(17):3448–3455. https://doi.org/10.7150/jca.21134
15. Braverman LE, Vagenakis A, Downs P, Foster AE, Sterling K, Ingbar SH (1973) Effects of replacement doses of sodium L-thyroxine on the peripheral metabolism of thyroxine and triiodothyronine in man. J Clin Invest 52(5):1010–1017. https://doi.org/10.1172/jci107265
16. Yang F, Wei L, Huo X, Ding Y, Zhou X, Liu D (2018) Effects of early postoperative enteral nutrition versus usual care on serum albumin, prealbumin, transferrin, time to first flatus and postoperative hospital stay for patients with colorectal cancer: a systematic review and meta-analysis. Contemp Nurse 54(6):561–577. https://doi.org/10.1080/10376178.2018.1513809
17. Jia RR, Zhong JH, Huo RR, Su QB, Xiang X, Zhao FL, Qin ZB, Chen JH, Liao YY, Ma L, Xiang BD, Zhang CY, Li LQ (2019) Correlation between serum prealbumin and prognosis of patients with hepatocellular carcinoma after hepatectomy. J Surg Oncol 119(6):794–800. https://doi.org/10.1002/jso.25378
18. Tennent GA, Brennan SO, Stangou AJ, O'Grady J, Hawkins PN, Pepys MB (2007) Human plasma fibrinogen is synthesized in the liver. Blood 109(5):1971–1974. https://doi.org/10.1182/blood-2006-08-040956
19. Mosesson MW (2005) Fibrinogen and fibrin structure and functions. J Thromb Haemost 3(8):1894–1904. https://doi.org/10.1111/j.1538-7836.2005.01365.x
20. Arigami T, Okumura H, Matsumoto M, Uchikado Y, Uenosono Y, Kita Y, Owaki T, Mori S, Kurahara H, Kijima Y, Ishigami S, Natsugoe S (2015) Analysis of the fibrinogen and neutrophil-lymphocyte ratio in esophageal squamous cell carcinoma: a promising blood marker of tumor progression and prognosis. Medicine 94(42):e1702. https://doi.org/10.1097/md.0000000000001702
21. Son HJ, Park JW, Chang HJ, Kim DY, Kim BC, Kim SY, Park SC, Choi HS, Oh JH (2013) Preoperative plasma hyperfibrinogenemia is predictive of poor prognosis in patients with nonmetastatic colon cancer. Ann Surg Oncol 20(9):2908–2913. https://doi.org/10.1245/s10434-013-2968-8
22. Garcia MG, Bayo J, Bolontrade MF, Sganga L, Malvicini M, Alaniz L, Aquino JB, Fiore E, Rizzo MM, Rodriguez A, Lorenti A, Andriani O, Podhajcer O, Mazzolini G (2011) Hepatocellular carcinoma cells and their fibrotic microenvironment modulate bone marrow-derived mesenchymal stromal cell migration in vitro and in vivo. Mol Pharm 8(5):1538–1548. https://doi.org/10.1021/mp200137c
23. Zheng S, Shen J, Jiao Y, Liu Y, Zhang C, Wei M, Hao S, Zeng X (2009) Platelets and fibrinogen facilitate each other in protecting tumor cells from natural killer cytotoxicity. Cancer Sci 100(5):859–865. https://doi.org/10.1111/j.1349-7006.2009.01115.x
24. Ridker PM, Howard CP, Walter V, Everett B, Libby P, Hensen J, Thuren T (2012) Effects of interleukin-1beta inhibition with canakinumab on hemoglobin A1c, lipids, C-reactive protein, interleukin-6, and fibrinogen: a phase IIb randomized, placebo-controlled trial. Circulation 126(23):2739–2748. https://doi.org/10.1161/circulationaha.112.122556
25. Adam SS, Key NS, Greenberg CS (2009) D-dimer antigen: current concepts and future prospects. Blood 113(13):2878–2887. https://doi.org/10.1182/blood-2008-06-165845
26. Man YN, Wang YN, Hao J, Liu X, Liu C, Zhu C, Wu XZ (2015) Pretreatment plasma D-dimer, fibrinogen, and platelet levels significantly impact prognosis in patients with epithelial ovarian cancer independently of venous thromboembolism. Int J Gynecol Cancer 25(1):24–32. https://doi.org/10.1097/igc.0000000000000303
27. Batschauer AP, Figueiredo CP, Bueno EC, Ribeiro MA, Dusse LM, Fernandes AP, Gomes KB, Carvalho MG (2010) D-dimer as a possible prognostic marker of operable hormone receptor-negative breast cancer. Ann Oncol 21(6):1267–1272. https://doi.org/10.1093/annonc/mdp474
28. Yamamoto M, Yoshinaga K, Matsuyama A, Iwasa T, Osoegawa A, Tsujita E, Yamashita Y, Tsutsui S, Ishida T (2012) Plasma D-dimer level as a mortality predictor in patients with advanced or recurrent colorectal cancer. Oncology 83(1):10–15. https://doi.org/10.1159/000338329
29. Fukumoto K, Taniguchi T, Usami N, Kawaguchi K, Fukui T, Ishiguro F, Nakamura S, Yokoi K (2015) Preoperative plasma D-dimer level is an independent prognostic factor in patients with completely resected non-small cell lung cancer. Surg Today 45(1):63–67. https://doi.org/10.1007/s00595-014-0894-4

30. Liu P, Zhu Y, Liu L (2015) Elevated pretreatment plasma D-dimer levels and platelet counts predict poor prognosis in pancreatic adenocarcinoma. Onco Targets Ther 8:1335–1340. https://doi.org/10.2147/ott.s82329
31. Buller HR, van Doormaal FF, van Sluis GL, Kamphuisen PW (2007) Cancer and thrombosis: from molecular mechanisms to clinical presentations. J Thromb Haemost 5(Suppl 1):246–254. https://doi.org/10.1111/j.1538-7836.2007.02497.x