

Fibrinogen/Albumin Ratio as a Promising Marker for Predicting Survival in Pancreatic Neuroendocrine Neoplasms

This article was published in the following Dove Press journal:
Cancer Management and Research

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Background: The fibrinogen/albumin ratio (FAR) has been widely reported to be a possible biomarker for predicting prognosis in several types of tumors, but the prognostic value of the FAR in pancreatic neuroendocrine neoplasms (Pan-NENs) has not been systematically studied.

Patients and Methods: In total, 324 patients with Pan-NENs were recruited. The patients were divided into 2 subgroups according to the FAR cutoff value, and clinicopathological characteristics of the 2 subgroups were compared. Overall survival (OS) was the primary endpoint, and progression-free survival (PFS) was the secondary endpoint. The prognostic value of the FAR was analyzed in univariate and multivariate analyses.

Results: The optimal cutoff value for the FAR was calculated to be 0.08 for OS. The patients with a FAR ≥ 0.08 had higher proportions of nonfunctioning tumors, Pan-NECs, grade 3 tumors, and stage IV tumors than those with a FAR < 0.08 . In the univariate analysis, a FAR ≥ 0.08 was associated with poor OS (hazard ratio (HR) = 2.37, $P < 0.001$) and PFS (HR = 2.37, $P < 0.001$). In the multivariate analysis, a FAR ≥ 0.08 was an independent risk factor for poor OS (HR = 4.70, $P < 0.001$) and PFS (HR = 1.80, $P = 0.006$).

Conclusion: The pretreatment FAR, which includes fibrinogen and albumin, was a feasible and predictive biomarker for prognosis in patients with Pan-NENs. An elevated FAR, based on a cutoff value of 0.08, was an independent risk factor for poor OS and PFS.

Keywords: pancreatic neuroendocrine neoplasms, survival, fibrinogen/albumin ratio

Introduction

Pancreatic neuroendocrine neoplasms (Pan-NENs) are a relatively rare type of pancreatic tumor that accounts for only 1–2% of all pancreatic malignancies, but the Pan-NEN incidence is rapidly increasing.¹⁻³ In recent years, researchers have shown increasing interest in Pan-NENs. Pan-NENs are a heterogeneous disease with different prognoses in different subgroups.^{4,5} In addition to the existing tumor-node-metastasis (TNM) staging system,⁶ tumor grade,⁷ and differentiation status,⁸ there are a number of emerging markers for predicting the prognosis of patients with Pan-NENs, including the blood glucose level,⁹ peripheral blood neutrophil/lymphocyte ratio¹⁰ and some other peripheral blood test markers. However, no studies have explored the prognostic value of the fibrinogen/albumin ratio (FAR) in Pan-NENs.

Plasma fibrinogen is a soluble glycoprotein synthesized and secreted by liver cells and is an important protein involved in the processes of blood coagulation and hemostasis.¹¹ In the presence of ionized calcium, fibrinogen is converted into fibrin

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by thrombin.¹² As an “acute-phase reactant”, fibrinogen may play significant roles in various types of nonspecific stimuli, such as inflammation, pregnancy, and autoimmune diseases.^{13,14} Previous research has suggested that plasma fibrinogen may also play a pivotal role in the progression of various malignancies.^{15,16} Albumin is a circulating protein in the plasma and a nutritional indicator and can also participate in inflammation.¹⁷ Hypoalbuminemia is closely related to a low quality of life and has detrimental effects on therapeutic efficacy in cancer patients.^{18,19} Some studies have reported that the combination of fibrinogen and albumin can be used to predict the prognosis of cancer patients.^{20,21} The baseline FAR was found to be an independent prognostic factor in patients with esophageal squamous cell carcinoma,²⁰ soft tissue sarcoma,²¹ hepatocellular carcinoma,²² gastric cancer,²³ and so on. In addition, researchers found that a high FAR was significantly associated with deeper tumor infiltration, lymph node metastasis and distant metastasis.²⁴ To the best of our knowledge, no research has explored the prognostic value of the FAR in Pan-NENs.

Therefore, this study provides the first demonstration of an association between the FAR and survival in patients with Pan-NENs through a retrospective study involving 324 patients.

Patients and Methods

Patients and the Study Design

A retrospective follow-up study of Pan-NEN patients was conducted at the Shanghai Cancer Center, Fudan University, China, from January 2006 to December 2018. All enrolled patients were pathologically diagnosed based on histological or cytological evidence. According to the fifth edition of the World Health Organization (WHO) Classification of Tumors, Pan-NENs include well-differentiated pancreatic neuroendocrine tumors (Pan-NETs) and poorly differentiated neuroendocrine carcinomas (Pan-NECs).²⁵ The exclusion criteria were as follows: (1) patients without follow-up data; (2) patients with a second malignant tumor or multiple primary malignant tumors; (3) patients lacking albumin and fibrinogen data; (4) patients with clinical evidence of infection or other inflammatory diseases (patients with an abnormal white blood cell count or signs or symptoms of infectious disease); and (5) patients with liver cirrhosis and other severe hepatic diseases. The study was approved by the Ethics Committee of the Shanghai Cancer Center of Fudan University. All patients in the study agreed to the use of

their personal data for research purposes and provided written informed consent. The study was conducted according to the Declaration of Helsinki.

In total, 324 patients were recruited for our cohort. Clinicopathological patient data, including age, sex, tumor location, tumor grade, tumor differentiation, tumor stage, functioning tumors (yes or no), receipt of radical surgery (yes or no), and body mass index (BMI, < 18.5 or ≥ 18.5) were collected from medical records at the Shanghai Cancer Center. The tumor stage of each patient was based on the TNM staging for Pan-NENs established by the American Joint Committee on Cancer (AJCC), 8th edition. BMI was calculated based on the weight and height of patients on the day of admission, and according to guidelines of National Heart, Lung, and Blood Institute (NHLBI), we defined a BMI value less than 18.5 as low BMI. The levels of fibrinogen (g/L) and albumin (g/L) were obtained within 10 days prior to initial treatment.

Overall survival (OS), which was defined as the time from the first date of diagnosis to the date of death for any reason, was the primary endpoint. Patient OS data were ascertained through telephone follow-up. Progression-free survival (PFS), which was defined as the period from the onset of treatment to the observation of disease progression or death from any cause, was the secondary endpoint in this study. We evaluated patient disease progression according to the Response Evaluation Criteria in Solid Tumors (RECIST) (version 1.1) through imaging examinations (including computed tomography, magnetic resonance imaging, and positron emission tomography/computed tomography).²⁶ Due to differences in tumor stages and treatment options, the frequency of imaging examination varied. Normally, patients undergoing imaging are evaluated every three months during the course of treatment. The frequency of reexamination for patients who have undergone radical surgery but do not need other treatment is gradually reduced.

Statistical Methods

Statistical analyses were performed using SPSS 24.0 software (SPSS, Inc., Chicago, IL) and R Studio version 3.6.1. Receiver operating characteristic (ROC) curves with Youden's Index correction were established to determine the optimal cutoff threshold of the FAR for OS. We utilized a Kaplan-Meier survival curve with a 95% confidence interval (CI) for analyses of OS and PFS. Univariate and multivariate analyses were separately performed based on the Log rank test and the Cox proportional hazard model, respectively. Rank-sum tests, Pearson

χ^2 tests or Fisher's exact tests were used to compare clinicopathological characteristics between the groups. All *P* values were two sided, and *P* < 0.05 was considered statistically significant.

Results

Clinical Characteristics of the Enrolled Patients with Pan-NENs

A total of 324 patients were included in this study, and the mean follow-up time was 38.9 months. Selected clinical characteristics are shown in Table 1. Among the patients, 31 had Pan-NECs, and 293 had Pan-NETs; 69.4% (*n* = 225) of the patients were younger than 60 years old. The prevalence of females in the study was 56.2% (*n* = 182). A total of 126 (38.9%) patients had tumors located in the head of the pancreas, whereas 198 (61.1%) had tumors located in the body or tail of the pancreas. The prevalence of functioning tumors in the study was 10.5% (*n* = 34). Of the entire patient cohort, 238 (73.5%) patients underwent radical surgery, and 86 patients (26.5%) did not. A total of 124 (39.1%) patients had grade 1 Pan-NENs, 154 (48.6%) had grade 2 Pan-NENs, and 39 (12.3%) had grade 3 Pan-NENs. Moreover, 77 (23.8%) patients had stage I Pan-NENs, 117 (36.1%) had stage II Pan-NENs, 40 (12.3%) had stage III Pan-NENs, and 90 (27.8%) had stage IV Pan-NENs.

Correlations Between the FAR and Clinicopathological Factors

The median FAR was 0.072 (range 0.036–0.170), and the optimal cutoff value for the FAR was calculated to be 0.08 for OS. Then, Pan-NEN patients were divided into 2 subgroups based on whether their FAR was lower than the cutoff value (0.08). Differences in clinicopathological characteristics between the subgroups are shown in Table 1. The prevalence of patients with a FAR < 0.08 in the cohort was 70.4% (*n* = 228), and no significant differences in sex (*P* = 0.146), location (*P* = 0.934) and BMI (*P* = 0.946) were found. The proportions of functioning tumors, patients younger than 60 years, and well-differentiated Pan-NETs in the group of Pan-NEN patients with a FAR < 0.08 were higher than those in the group of patients with a FAR ≥ 0.08. Notably, the distribution of populations with different tumor stages was significantly different between the two subgroups (*P* = 0.001). The proportion of patients with stage IV disease in the group of patients with a FAR ≥ 0.08 was 1.99 times that of the group of patients with a FAR < 0.08 (42.7% vs 21.5%). It is worth noting that 18 (18.8%) patients with

Table 1 Clinicopathological Characteristics of All Patients

Variables	<i>n</i>	FAR < 0.08	FAR ≥ 0.08	<i>P</i>
Total	324	228	96	
Age (years), <i>n</i> (%)				0.001
< 60	225	171 (75.0)	54 (56.3)	
≥ 60	99	57 (25.0)	42 (43.7)	
Sex, <i>n</i> (%)				0.146
Female	182	134 (58.8)	48 (50.0)	
Male	142	94 (41.2)	48 (50.0)	
Location, <i>n</i> (%)				0.934
Head	126	89 (39.0)	37 (38.5)	
Body or tail	198	137 (61.0)	59 (61.5)	
Functioning tumors, <i>n</i> (%)				<0.001
Yes	34	33 (13.9)	1 (1.6)	
No	290	195 (86.1)	95 (98.4)	
Tumor grade, <i>n</i> (%) ^a				0.032
Grade 1	124	94 (42.5)	30 (31.3)	
Grade 2	154	106 (48.0)	48 (50.0)	
Grade 3	39	21 (9.5)	18 (18.8)	
Tumor stage, <i>n</i> (%)				0.001
I	77	62 (27.2)	15 (15.6)	
II	117	86 (37.7)	31 (32.3)	
III	40	31 (13.6)	9 (9.4)	
IV	90	49 (21.5)	41 (42.7)	
Tumor differentiation, <i>n</i> (%)				0.046
Well	293	211 (92.5)	82 (85.4)	
Poor	31	17 (7.5)	14 (14.6)	
Radical surgery, <i>n</i> (%)				<0.001
Yes	238	181 (79.4)	57 (59.4)	
No	86	47 (20.6)	39 (40.6)	
Body mass index, <i>n</i> (%) ^b				0.946
<18.5	21	15 (6.9%)	6 (6.7%)	
≥18.5	287	203 (93.1%)	84 (93.3%)	

Notes: ^aData of tumor grade for 7 patients with were missing; ^bdata of body mass index for 16 patients were missing.

Abbreviation: FAR, fibrinogen/albumin ratio.

a FAR ≥ 0.08 and 21 (9.5%) patients with a FAR < 0.08 had tumors that were classified as grade 3, and this difference was nearly two-fold. Furthermore, the majority of patients with a FAR < 0.08 ($n=181$, 79.4%) underwent radical surgery, whereas only 57 (59.4%) patients with a FAR ≥ 0.08 underwent radical surgery ($P < 0.001$).

Association Between the FAR and Survival in Patients with Pan-NENs

At the end of the follow-up period, 14.5% of the participants ($n = 47$) had died, and 36.9% ($n = 116$) had disease progression (10 participants had no data on recurrence). Briefly, a FAR ≥ 0.08 was associated with poorer OS ($P < 0.001$, Figure 1) and PFS ($P < 0.001$, Figure 2) than a FAR < 0.08 . The relationships between clinicopathological variables and OS are presented in Table 2. In a univariate analysis, variables such as grade 2 tumors (hazard ratio (HR) = 3.92, $P = 0.006$), grade 3 tumors (HR = 20.04, $P < 0.001$), stage III tumors (HR = 16.91, $P = 0.008$), stage IV tumors (HR = 45.47, $P < 0.001$), no receipt of radical surgery (HR = 8.14, $P < 0.001$), and a FAR ≥ 0.08 (HR = 3.87, $P < 0.001$) were risk factors for poor OS in patients with Pan-NENs. In a multivariate analysis, and a FAR ≥ 0.08 (HR = 4.70, $P < 0.001$), along with variables such as tumors located in the head of the pancreas, grade 3 tumors and stage IV tumors, were independent risk factors for poor OS. Survival was significantly poorer for the patients with a FAR ≥ 0.08 than those with a FAR < 0.08 , as shown in Figure 1 ($P < 0.001$).

Three hundred fourteen of the enrolled patients provided the necessary information for the determination of PFS. The relationships between clinicopathological variables and PFS are presented in Table 3. In a univariate analysis,

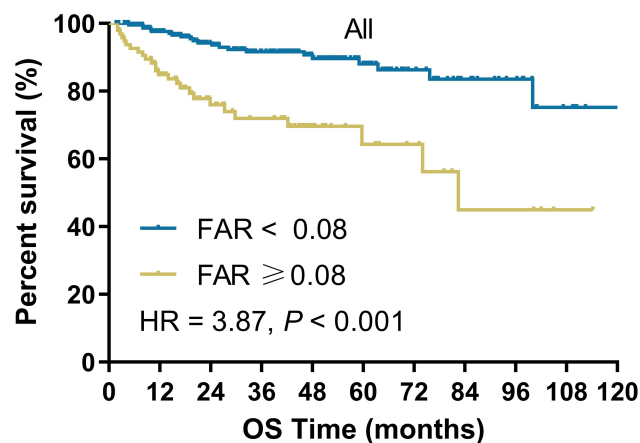


Figure 1 Kaplan-Meier plot of OS for all patients stratified into two groups: patients with a FAR ≥ 0.08 and patients with a FAR < 0.08 .

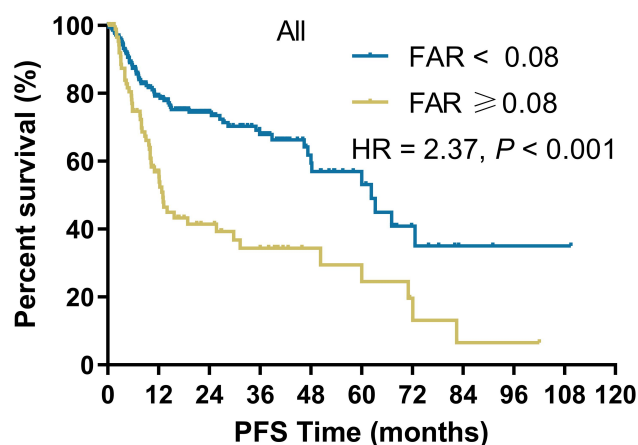


Figure 2 Kaplan-Meier plot of PFS for all patients stratified into two groups: patients with a FAR ≥ 0.08 and patients with a FAR < 0.08 .

relatively poor PFS was significantly correlated with female sex (HR = 1.45, $P = 0.050$), a tumor located in the body or tail of the pancreas (HR = 1.48, $P = 0.048$), functioning tumors (HR = 2.63, $P = 0.021$), grade 2 tumors (HR = 3.61, $P < 0.001$), grade 3 tumors (HR = 10.66, $P < 0.001$), stage II tumors (HR = 6.06, $P = 0.014$), stage III tumors (HR = 15.99, $P < 0.001$), stage IV tumors (HR = 71.57, $P < 0.001$), no receipt of radical surgery (HR = 8.93, $P < 0.001$), BMI ≥ 18.5 (HR = 2.30, $P = 0.013$) and a FAR ≥ 0.08 (HR = 2.37, $P < 0.001$). A multivariate analysis revealed a FAR ≥ 0.08 (HR = 1.73, $P = 0.007$), along with grade 3 tumors and stage II, III & IV tumors, were independent prognostic factors for unfavorable PFS. The median PFS time was 32.5 months in the patients with a FAR ≥ 0.08 and 61.7 months in the patients with a FAR < 0.08 .

Moreover, we also analyzed the subgroup of patients who underwent radical surgical resection ($n = 238$). Likewise, FAR value > 0.08 was also associated with unfavorable overall survival ($P = 0.042$, Figure 3) and progression-free survival ($P = 0.002$, Figure 4) for patients who underwent radical surgical resection.

Discussion

Pan-NENs are rare heterogeneous tumors, and their biological behavior is incompletely defined.⁴ With advancements in imaging technology, the detection rate of pancreatic neuroendocrine tumors is increasing in many parts of the world.²⁷ This study attempted to explore the prognostic value of the FAR in Pan-NENs. Fibrinogen is not only an important component in the coagulation cascade but also an acute-phase reactant associated with inflammation.¹³ Recently, there has been increasing evidence that fibrinogen plays important roles in tumor-related biological behaviors such

Table 2 Univariate and Multivariate Analyses for the Overall Survival of All Patients According to Their Baseline FAR

Variables	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	P	HR	95% CI	P
Age (years)						
< 60	1			1		
≥ 60	0.99	0.53–1.85	0.973	0.861	0.431–1.72	0.671
Sex						
Female	1			1		
Male	0.64	0.36–1.13	0.125	1.716	0.855–3.446	0.129
Location						
Head	1			1		
Body or tail	0.82	0.46–1.47	0.506	0.347	0.173–0.694	0.003
Functioning tumors						
Yes	1			1		
No	0.15	0.02–1.08	0.059	0.836	0.101–6.924	0.868
Tumor grade						
Grade 1	1			1		
Grade 2	3.92	1.48–10.36	0.006	5.498	1.197–25.245	0.028
Grade 3	20.04	7.49–53.63	<0.001	16.377	3.313–80.953	0.001
Tumor stage						
I	1			1		
II	2.80	0.33–24.02	0.347	1.120	0.109–11.45	0.924
III	16.91	2.08–137.72	0.008	3.612	0.376–34.682	0.266
IV	45.47	6.21–333.12	<0.001	7.792	0.759–80.04	0.084
Radical surgery						
Yes	1			1		
No	8.14	4.43–14.97	<0.001	2.813	0.921–8.586	0.069
Body mass index						
<18.5	1			1		
≥18.5	0.443	0.173–1.131	0.089	1.504	0.559–4.047	0.419
FAR						
<0.08	1			1		
≥0.08	3.87	2.17–6.90	<0.001	4.56	2.306–9.567	<0.001

Abbreviations: HR, hazard ratio; FAR, fibrinogen/albumin ratio.

as epithelial-mesenchymal transition, cell proliferation, and angiogenesis.²⁸ Fibrinogen can promote tumor cell adhesion and invasion by providing a stable framework for the tumor

extracellular matrix.²⁹ In addition, an important link has been established between this hemostatic factor and innate immunity. Platelets and fibrinogen can increase the metastatic

Table 3 Univariate and Multivariate Analyses for the Progression-Free Survival of All Patients According to Their Baseline FAR

Variables	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	P	HR	95% CI	P
Age (years)						
< 60	1			1		
≥ 60	1.02	0.69–1.52	0.916	0.677	0.436–1.052	0.083
Sex						
Female	1			1		
Male	0.69	0.48–1.00	0.050	0.743	0.493–1.121	0.157
Location						
Head	1			1		
Body or tail	1.48	01.00–2.19	0.048	1.090	0.705–1.685	0.700
Functioning tumors						
Yes	1			1		
No	0.38	0.17–0.86	0.021	0.876	0.537–2.148	0.772
Tumor grade						
Grade 1	1			1		
Grade 2	3.61	2.12–6.15	<0.001	1.491	0.789–2.818	0.219
Grade 3	10.66	5.87–19.37	<0.001	1.920	0.919–4.011	0.083
Tumor stage						
I	1			1		
II	6.06	1.43–25.62	0.014	4.969	1.138–21.704	0.033
III	15.99	3.68–69.59	<0.001	7.579	1.613–35.613	0.010
IV	71.57	17.45–293.53	<0.001	27.168	5.524–133.621	<0.001
Radical surgery						
Yes	1			1		
No	8.93	6.02–13.24	<0.001	1.827	0.88–6.07	0.072
Body mass index						
<18.5	1			1		
≥18.5	0.434	0.225–0.837	0.013	0.796	0.399–1.586	0.516
FAR						
<0.08	1			1		
≥0.08	2.37	1.64–3.42	<0.001	1.803	1.185–2.744	0.006

Abbreviations: HR, hazard ratio; FAR, fibrinogen/albumin ratio.

potential of tumors by preventing natural killer cells from eliminating tumor cells.³⁰ Moreover, there is a close relationship between fibrinogen and systemic inflammation. Many

studies have reported that plasma fibrinogen levels are positively correlated with many inflammation scores, such as the neutrophil/lymphocyte ratio, platelet/lymphocyte ratio and

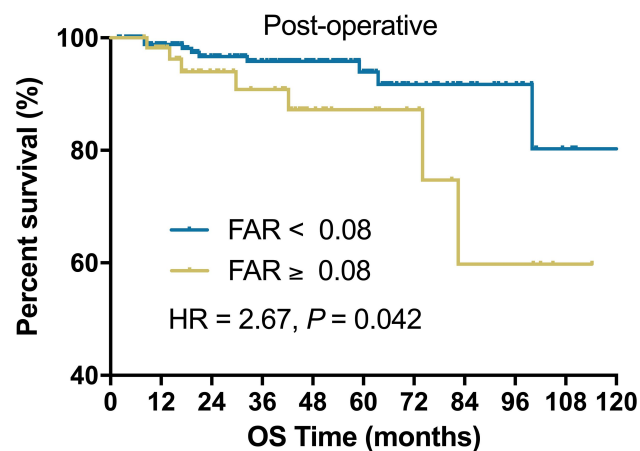


Figure 3 Kaplan–Meier plot of OS for patients without radical surgical resection stratified into two groups: patients with a FAR ≥ 0.08 and patients with a FAR < 0.08.

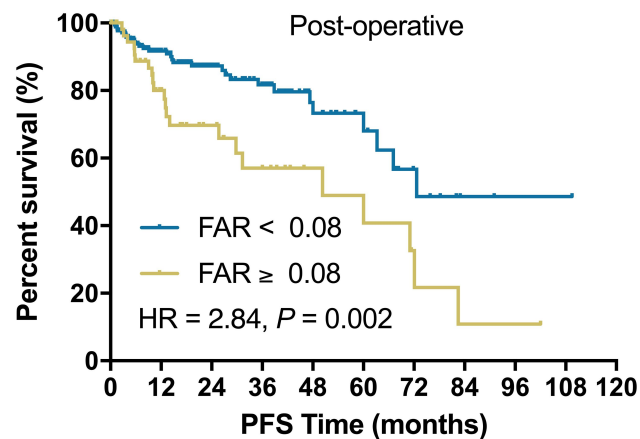


Figure 4 Kaplan–Meier plot of PFS for patients without radical surgical resection stratified into two groups: patients with a FAR ≥ 0.08 and patients with a FAR < 0.08.

lymphocyte/monocyte ratio.^{23,31} Fibrinogen can also induce the synthesis of interleukin 6 to promote tumor progression.³²

Albumin is the most abundant circulating protein in the plasma and is not only a nutritional indicator but can also be involved in the inflammatory response.¹⁷ When the body is in an inflamed or malnourished state, albumin synthesis is significantly reduced.^{33,34} Hypoalbuminemia may cause impairment in the immune function of tumor patients, reduce therapeutic effects, and increase mortality.³⁵ Additionally, many studies have shown that hypoalbuminemia is an independent risk factor for a poor prognosis in many cancers.³⁶ The FAR can potentially represent the inflammatory status and nutritional status of the body. Many studies have shown that an elevated FAR is closely related to a poor prognosis in various cancers.³⁷

To the best of our knowledge, our study is the first to report on the prognostic role of the FAR in Pan-NENs.

In this study, a total of 324 patients with Pan-NENs were enrolled. The cutoff value for the FAR was calculated to be 0.08 for OS, and the patients were divided into two groups according to whether their FAR was lower than 0.08. Surprisingly, the two groups presented different characteristics: the patients with a FAR ≥ 0.08 had higher proportions of nonfunctioning tumors, Pan-NECs, grade 3 tumors, and stage IV tumors than the patients with a FAR < 0.08. This suggests that patients with a relatively high FAR may be more prone to invasion and metastasis. Additionally, the patients with a FAR ≥ 0.08 at the time of study enrollment exhibited worse OS and PFS than the patients with a FAR < 0.08. In univariate and multivariate analyses, a FAR ≥ 0.08 was associated with poor OS and PFS. The median PFS time in the patients with a FAR < 0.08 was 1.90 times that of the patients with a FAR ≥ 0.08. An elevated FAR is an independent risk factor for a poor prognosis in patients with Pan-NENs.

There are also some limitations to this research. As a retrospective, single-center study, these results require validation through multiple neutral prospective studies. Second, differences in patient treatments might lead to confusion with regard to the results. In addition, due to an insufficient follow-up time period, the median survival time could not be calculated.

Despite these limitations, our study is the first to show that the pretreatment FAR, which includes both fibrinogen and albumin, is a feasible and predictive biomarker for prognosis in patients with Pan-NENs. An elevated FAR, as defined by a cutoff value of 0.08, was an independent risk factor for poor OS and PFS.

Acknowledgment

This work was supported by the National Natural Science Foundation of China (grant numbers 81625016, 81871940, 81902417), the Scientific Innovation Project of Shanghai Education Committee (2019-01-07-00-07-E00057), Clinical and Scientific Innovation Project of Shanghai Hospital Development Center (SHDC12018109), the Shanghai Natural Science Foundation (grant number 17ZR1406300), the Shanghai Cancer Center Foundation for Distinguished Young Scholars (grant number YJJQ201803), and the Fudan University Personalized Project for “Double Top” Original Research (grant number XM03190633).

Disclosure

The authors report no conflicts of interest for this work.

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