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Predictive value of serum actinin-4, TFF1, and TGFBI for the prognosis of patients with hepatocellular carcinoma after transarterial chemoembolization

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Abstract: Objective To investigate the predictive value of serum actinin-4, trefoil factor 1 (TFF1), and transforming growth factor-β-induced (TGFBI) protein for the prognosis of patients with hepatocellular carcinoma (HCC) after transarterial chemoembolization (TACE). **Methods** From January 2020 to January 2023, 312 patients with HCC who underwent TACE in Shijiazhuang People's Hospital were collected as the study From January 2020 to January 2023, 312 patients with HCC who underwent TACE in Shijiazhuang People's Hospital were collected as the study subjects (HCC group), patients with PHC were separated into a good prognosis group (n=252) and a poor prognosis group (n=60) based on their postoperative conditions, another 312 patients who underwent health examinations were collected as the control group. Serum levels of actinin-4, TFF1, and TGF1 were measured in the control group. Serum levels of actinin-4, TFF1, and TGFBI were detected by ELISA. Logistic regression was applied to analyze the influencing factors of poor prognosis in patients with HCC after TACE. Logistic regression was applied to analyze the influencing factors of poor prognosis in patients with HCC after TACE. Receiver operating characteristic curve (ROC) was applied to analyze the predictive value of serum actinin-4, TFF1, and TGFBI for poor prognosis after TACE in patients with HCC. **Results** There was no obvious difference in gender, age, Child-Pugh grade, and clinical stage between the group with good prognosis and the group with poor prognosis. prognosis and the group with poor prognosis (P>0.05), but there were statistically differences in tumor size and portal vein tumor thrombus (P<0.05). Compared with control group, the serum levels of actinin-4 [(45.67±10.23) pg/mL vs (28.25±6.96) pg/mL, t=24.868, P<0.01], TFF1 [(5.04±1.53) ng/mL vs (2.32±0.64) ng/mL, t=28.969, P<0.01], TGFBI [(19.16±4.36) ng/mL vs (10.25±2.43) ng/mL, t=31.530, P<0.01] were obviously higher in the HCC group . Compared with the group with good prognosis, the serum levels of actinin-4, TFF1, and TGFBI in the group with poor prognosis were obviously increased (P<0.01). The results of multivariate logistic regression analysis showed that tumor size, portal vein tumor thrombus, serum actinin-4, TFF1, and TGFBI were all influencing factors for poor prognosis of patients with PHC after TACE (P<0.05). ROC curve results showed that the combined prediction of serum actinin-4, TFF1, and TGFBI for poor prognosis after TACE in HCC patients had an AUC of 0.926, a sensitivity of 81.3%. a sensitivity of 81.3%, and a specificity of 76.8%. **Conclusion** The serum levels of actinin-4, TFF1, and TGFBI in patients with poor prognosis after TACE for HCC are obviously increased, and the combined determination of the three has good predictive value for prognosis of patients.

Keywords: Primary hepatocellular carcinoma; Transarterial chemoembolization; Actinin-4; Trefoil factor 1; Transforming growth factor-β-induced protein

Primary hepatocellular carcinoma (PHC) is one of the common malignant tumors in the digestive system, and its early symptoms are not obvious, and most of the patients have already been in the middle or late stage when they consult the doctor, missing the best time for surgical treatment[1]. At this time, transarterial chemoembolization (TACE) via catheter is the first choice for patients with PHC. TACE is simple to operate, blocking the blood supply of the tumor through embolizing agent and prompting ischemic necrosis of the tumor tissues to achieve the therapeutic purpose[2]. However, some patients with PHC may develop intrahepatic metastasis or recurrence of tumor cells after TACE[3-4]. Therefore, it is necessary to predict the poor prognosis of patients with PHC after TACE effectively. As an actin-binding protein, actinin-4 is involved in reconstruction of cytoskeleton, cell adhesion and morphology regulation. It is closely related to tumor-cell invasion and migration[5]. Trefoil factor 1 (TFF1) is one of the gastric mucoprotective factors, which plays an important role in the repair process of gastrointestinal mucosal damage and is abnormally expressed in a variety of malignant tumors[6]. Transforming growth factor-β-induced protein (TGFBI) is secreted by transforming growth factor-β, which can promote epithelial-mesenchymal transition in gastric cancer cells and is closely related to tumor recurrence and metastasis[7]. Previous studies have shown that actinin-4, TFF1, and TGFBI all play important roles in the development of gastric cancer[5-7]. Therefore, the three protein may have a specific predictive value for the prognosis of patients with PHC after TACE. Based on this, the aim of this study was to investigate the predictive value of serum actinin-4, TFF1, and TGFBI on the prognosis of patients with PHC after TACE, and to provide a reference for the improvement of the prognosis

of patients with PHC.

1 Materials and methods

1.1 General information

Three hundred and twelve patients with PHC who were underwent TACE at Shijiazhuang People's Hospital from January 2020 to January 2023 were selected for the study (PHC group), including 188 males and 124 females, aged 40-72 (55.75±6.13) years.

Inclusion criteria: (1) meeting the diagnostic criteria related to PHC[8], and confirmed by liver tissue biopsy; (2) all meeting the indications for TACE treatment; (3) undergoing TACE treatment for the first time; (4) Child-Pugh grading of grade A or B; (5) clinical staging II-III; (6) complete clinical data of patients.

Exclusion criteria: (1) combination of other malignant tumors; (2) the presence of previous history of liver surgery; (3) the presence of liver metastasis; (4) abnormal immune function; (5) contraindication to interventional therapy; and (6) the expected *survival* time was less than 6 months. Another 312 cases were selected as the control group from those who underwent health examination in Shijiazhuang People's Hospital during the same period. Among them, 182 cases were male, 130 cases were female, and their ages ranged from 40 to 73 (55.25±6.27) years old, and the differences between the PHC group and the control group were not statistically significant in terms of gender and age (P>0.05). This study was reviewed and approved by the Ethics Committee of the hospital.

1.2 Methods

1.2.1 Serum actinin-4, TFF1, TGFBI levels

A total of 5 mL of fasting elbow venous blood was drawn from patients with PHC before treatment and the control group on the day of physical examination, centrifuged at 3,500 r/min for 15 min and the supernatant was separated, packed in EP tubes and refrigerated at -80 ℃ to be measured. The levels of serum actinin-4, TFF1 and TGFBI were determined by ELISA, the absorbance of different concentrations of standard solutions at 450 nm was measured by ELISA and a standard curve was plotted, the absorbance of each sample was measured, and the levels of serum actinin-4, TFF1 and TGFBI were calculated according to the standard curves. Actininin-4 and TGFBI kits were supplied by Shanghai Enzyme-linked Biotechnology Co., Ltd. (Batch No. ml063245, ml061150), and TFF1 kit was provided by Abcam (Lot Number: ab277718).

1.2.2 Short-term prognostic assessment

At the patient's follow-up visit 4 weeks after surgery, an enhanced CT or MRI was performed to measure all target lesions, and the patient's short-term prognosis was assessed according to Solid Tumor RECIST gudielines (version 1.0)[9]: (1) complete remission: disappearance of the solid lesions in the target area after TACE treatment and maintained for more than 4 weeks; (2) partial remission: the sum of the largest diameters of the lesions was reduced by more than 30% compared with the baseline level and maintained for more than 4 weeks; (3) stable disease: no new lesions appeared, and the sum of the diameters of the solid lesions was reduced by less than 30% compared with the baseline level, or increased by less than 20%; and (4) disease progression: the emergence of new lesions or an increase of the sum of the largest diameters of the lesions by more than 20%. Patients with complete and partial remission were included in the good prognosis group (n=252), and patients with stable disease and disease progression were included in the poor prognosis group (n=60).

1.3 Statistical methods

SPSS 25.0 statistical software was used for statistical analysis. Normally distributed measurement data were expressed by $\bar{x} \pm s$, and differences between the 2 groups were compared using the group t-test. Enumeration data were described by cases, and comparisons were performed with the Chi-square test. Multivariate logistic regression was used to analyze the factors influencing the poor prognosis of TACE in patients with PHC. The ROC curve analyzed the predictive value of serum actinin-4, TFF1, and TGFBI for the poor prognosis of patients with PHC following TACE. The predictive value of poor prognosis of patients with PHC by actinin-4, TFF1, and TGFBI was analyzed by comparing the area under the ROC curve of actinin-4, TFF1, and TGFBI in combination with the area under the ROC curve of the three independently predicting the prognosis of the patients by the Z-test. P<0.05 indicates statistically significant differences.

2 Results

2.1 Comparison of general information between the good prognosis group and the poor prognosis group

The difference between the good prognosis group and the poor prognosis group was not statistically significant in terms of gender, age, Child-Pugh classification, and clinical staging (P>0.05). The number of cases of patients with tumors ≥ 5 cm and with portal vein tumor thrombosis in the poor prognosis group was more than that in the good prognosis group (P < 0.05). **[Table 1]**

2.2 Comparison of levels in serum actinin-4, TFF1, TGFBI

Compared with the control group, serum actinin-4, TFF1, and TGFBI levels of patients in the PHC group were significantly higher (P<0.05). **[Table 2]** The serum actinin-4, TFF1, and TGFBI levels of patients in the poor

prognosis group were significantly higher than those in the good prognosis group (P<0.05). **[Table 3]**

2.3 Logistic regression of factors affecting poor prognosis after TACE in patients with PHC

The prognostic status of patients with PHC after TACE was used as the dependent variable (poor prognosis = 1, good prognosis = 0). Tumor size (<5 cm = 0, ≥5 cm = 1), portal vein tumor thrombosis (yes = 1, no = 0), serum actinin-4, TFF1, TGFBI levels (all measured values) were used as independent variables for multivariate logistic regression. The results showed that tumor size, portal vein tumor thrombosis, and serum actinin-4, TFF1, and TGFBI were influential factors in the prognosis of patients with PHC after TACE (P < 0.05). **[Table 4]**

Tab.1 Comparison of general information between the good prognosis group and the poor prognosis group (case)

Item	Good prognosis group (n=252)	Poor prognosis group (n=60)	χ^2 value	P value
Gender				
Male	148	40	1.275	0.259
Female	104	20		
Age				
<55 years	134	25	2.568	0.109
≥55 years	118	35		
Child-Pugh classification				
A	145	33	0.128	0.721
B	107	27		
Tumor size				
<5 cm	154	26	6.275	0.012
≥5 cm	98	34		
clinical staging				
Phase II	144	28	2.150	0.143
Phase III	108	32		
Portal vein tumor thrombosis	113	38	6.636	0.010

Tab. 2 Comparison of serum actinin-4, TFF1, and TGFBI levels between the PHC group and the control group ($\bar{x} \pm s$)

Groups	Cases	Actinin-4 (pg/mL)	TFF1 (ng/mL)	TGFBI (ng/mL)
Control group	312	28.25 ± 6.96	2.32 ± 0.64	10.25±2.43
PHC group	312	45.67±10.23	5.04 ± 1.53	19.16±4.36
***t* value**		24.868	28.969	31.530
***P* value**		<0.001	<0.001	<0.001

Tab.3 Comparison of serum actinin-4, TFF1, and TGFBI levels between the group with good prognosis and the group with poor prognosis ($\bar{x} \pm S$)

Groups	Cases	Actinin-4 (pg/mL)	TFF1 (ng/mL)	TGFBI (ng/mL)
Good prognosis group	252	43.02±10.32	4.62±1.38	18.12±4.15
Poor prognosis group	60	56.81±9.86	6.78±2.15	23.52±5.24
***t* value**		9.380	9.663	8.586
***P* value**		<0.001	<0.001	<0.001

Tab.4 Logistic regression of factors affecting poor prognosis after TACE in patients with PHC

Item	β	*SE*	*Wald*χ^2	*P* value	*HR*	95% *CI*
Tumor size	0.305	0.143	4.557	0.033	1.357	1.025-1.796
Portal vein tumor thrombus	0.393	0.155	6.442	0.011	1.482	1.094-2.008
Actinin-4	0.551	0.161	11.713	0.001	1.735	1.265-2.379
TFF1	0.490	0.159	9.513	0.002	1.633	1.196-2.230
TGFBI	0.722	0.221	10.665	0.001	2.058	1.335-3.174

2.4 Predictive value of serum actinin-4, TFF1 , TGFBI on prognosis after TACE in patients with PHC

The results of ROC curves showed that actinin-4 predicted poor prognosis after TACE in patients with PHC with an AUC of 0.811 (95% CI: 0.750-0.872). The sensitivity and specificity were 83.3% and 62.3%, respectively, and the cut-off value was 49.98 pg/mL. TFF1 predicted poor prognosis after TACE in patients with PHC had an AUC of 0.829 (95% CI: 0.761-0.897), had a sensitivity and specificity of 83.3%, 65.4%, and a cut-off value of 5.92 ng/mL. TGFBI predicted poor prognosis after TACE in patients with PHC. The AUC for predicting poor prognosis after TACE

in patients with PHC was 0.822 (95% CI: 0.755-0.888), the sensitivity and specificity were 83.3% and 63.5%, respectively, and the cut-off value was 21.48 ng/mL. The AUC for predicting poor prognosis after TACE in patients with PHC by combining the three was 0.926 (95% CI: 0.889-0.963), the sensitivity was 81.3%, and the specificity was 76.8%. The AUC predicted by the combination of the three was significantly greater than the AUC predicted by actinin-4 alone (Z=3.162, P=0.002), TFF1 alone (Z=2.436, P=0.015), and TGFBI alone (Z=2.670, P=0.008). **[Figure 1]**

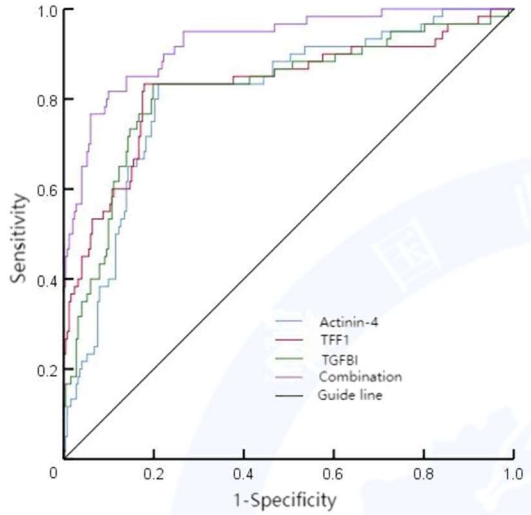

Fig. 1 ROC curve for predicting poor prognosis after TACE in patients with PHC

3 Discussion

Patients with PHC do not have specific symptoms in the early stage, so most of them are already in the middle and advanced stages when diagnosed, which misses the perfect time for surgical treatment[10]. TACE is a commonly used clinical treatment method that can better reduce the tumor's size and improve patients' clinical symptoms. It is suitable for middle or advanced-stage patients with PHC who cannot undergo surgery to remove tumor [11]. However, the hypoxic microenvironment generated during TACE is conducive to tumor cell growth, formation of new blood vessels, and alteration of bioactive substances associated with matrix degradation, which leads to tumor recurrence or metastasis, thus seriously affecting the prognosis of patients[12]. Currently, the prognosis of patients undergoing cancer treatment is mainly assessed by imaging techniques, which can be used to evaluate the prognosis of patients by observing the changes in the target lesions. However, this method is affected by various influential factors and has no predictive value because it is difficult to show the blood flow inside the tumor[13].

Actinin-4 is an actin-binding protein and a component of the cytoskeleton, with an actin-binding domain at the N-terminal end, which can cross-link with actin to maintain cellular structure and enhance cellular motility[14]. Previous studies have shown that actinin-4 is closely related to tumor invasion and metastasis, and can be used as a marker for various malignant tumors[15]. Fang *et al.*[16] showed that the serum levels of actinin-4 in breast cancer patients were significantly higher than those in healthy controls, and had a good predictive value of the clinical outcomes of breast cancer patients. The results of this study showed that serum actinin-4 levels in patients with PHC were significantly higher than those in the control group, and the trend of the level change was consistent with the results of the above study. Further analysis showed that the serum actinin-4 levels of patients in the poor prognosis group were significantly higher than those in the good prognosis group, suggesting that actinin-4 may be involved in the development and tumor progression of PHC. The reasons may be due to the fact that actinin-4 can promote the phenotype transformation and epithelial-mesenchymal transformation of tumor cells, which promotes the tumor invasion and metastasis. Overexpression of actinin-4 leads to the increase of the invasion and metastasis of tumor cells by interacting with actin cytoskeleton, which promotes the development of patients' poor prognosis The results of the multivariate logistic regression analysis showed tha high expression of actinin-4 was an independent risk factor for poor prognosis of patients with PHC. Therefore, the prognosis of patients can be evaluated by determining the expression of serum actinin-4 in patients with PHC.

TFF1 is a small polypeptide mainly derived from gastrointestinal mucosal cells belonging to one of the trilobal factor family members. Previous studies have shown that TFF1 is a key oncogene, which is highly expressed in the serum or tissues of patients with a variety of malignant tumors and is closely related to tumor cell proliferation and apoptosis, and is also involved in the metastasis and vascularization of tumor cells[17-18]. Hu et al.[19] found that serum TFF1 levels were significantly higher in breast cancer patients than in healthy controls, and its expression level was closely related to the clinical stage of patients. In this study, serum TFF1 levels in patients with PHC were significantly higher than those in the control group, and the poor prognosis group was significantly higher than the good prognosis group. The results of this study are consistent with the findings of Zhang [20] *et al.* in the serum of patients with PHC, which initially suggest that serum TFF1 may be involved in the development and progression of PHC. When the expression level of TFF1 is elevated, the expression of cell cycle protein D1 also increases in cells, promoting cell proliferation and tumor development. TFF1 also promotes cell detachment and tumor angiogenesis, which in turn promotes the infiltration and metastasis of tumor cells[17]. In addition, a high level of TFF1 is an independent risk factor for poor prognosis after TACE in patients with PHC, which is almost consistent with the results of Zhang[20] *et al.*

TGFBI can be directly involved in a variety of clinical diseases, such as malignant tumors, diabetes mellitus, corneal dystrophy, etc.[21]. Fico *et al.*[22] showed that TGFBI was highly expressed in patients with

breast cancer, and it could be involved in breast cancer progression and metastasis by regulating the mechanism of tumor hypoxia in breast cancer. This study showed that serum TGFBI levels were significantly higher in patients with PHC than in the control group, and were significantly higher in the poor prognosis group than in the good prognosis group. TGFBI is an extracellular matrix molecule that can activate matrix metalloproteinases by binding to adhesins or promoting neovascularization, thus promoting tumor cell invasion and metastasis. In addition, this study showed that the survival prognosis of patients with high TGFBI expression was poor, and serum TGFBI was an influential factor in the poor prognosis of patients with PHC, suggesting that TGFBI could be used as a tumor marker for the prognosis determination of patients with PHC. The ROC results showed that serum actinin-4, TFF1, and TGFBI predicted the poor prognosis of patients with PHC after TACE with high predictive efficacy, and the highest predictive value was found when they were detected in combination.

In summary, actinin-4, TFF1, and TGFBI were highly expressed in the serum of patients with poor prognosis after TACE for PHC. All three have a specific predictive value for patients' poor prognosis, and the combined predictive value is higher. However, this study has some limitations, as it is a single-center experiment and does not dynamically monitor the levels of patients' serum actinin-4, TFF1, and TGFBI. In the future, we can dynamically monitor the changes in the levels of patients' serum actinin-4, TFF1, and TGFBI and further validate the conclusions of this study with prospective, multicenter experiments.

Conflict of interest None

Reference

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·论　著·

血清 actinin-4、TFF1 及 TGFBI 水平对原发性肝癌患者经导管动脉化疗栓塞术后预后的预测

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摘要：目的　探讨血清辅肌动蛋白 4(actinin-4)、三叶因子 1(TFF1)、转化生长因子 β 诱导蛋白(TGFBI)对原发性肝癌(PHC)患者经导管动脉化疗栓塞(TACE)术后预后的预测价值。**方法**　以 2020 年 1 月至 2023 年 5 月在石家庄市人民医院进行 TACE 治疗的 312 例 PHC 患者为研究对象(PHC 组)，根据患者术后情况将 PHC 患者分为预后良好组(n=252)和预后不良组(n=60)，另选取同期行健康检查者 312 例为对照组。ELISA 法测定所有受试者血清 actinin-4、TFF1、TGFBI 水平。Logistic 回归分析 PHC 患者 TACE 术后预后不良的影响因素；受试者工作特征曲线(ROC)分析血清 actinin-4、TFF1、TGFBI 对 PHC 患者 TACE 术后预后不良的预测价值。**结果**　预后良好组与预后不良组在性别、年龄、Child-Pugh 分级及临床分期上差异无统计学意义(P>0.05)，在肿瘤大小、门静脉癌栓上差异有统计学意义(P<0.05)。与对照组相比，PHC 组患者血清 actinin-4[(45.67±10.23) pg/mL *vs* (28.25±6.96) pg/mL，t=24.868，P<0.01]、TFF1[(5.04±1.53) ng/mL *vs* (2.32±0.64) ng/mL，t=28.969，P<0.01]、TGFBI[(19.16±4.36) ng/mL *vs* (10.25±2.43) ng/mL，t=31.530，P<0.01]水平更高。与预后良好组相比，预后不良组患者血清 actinin-4、TFF1、TGFBI 水平均显著升高(P<0.01)。多因素 logistic 回归分析结果显示，肿瘤大小、门静脉癌栓、血清 actinin-4、TFF1、TGFBI 均为 PHC 患者 TACE 术后预后的影响因素(P<0.05)。ROC 曲线结果显示，血清 actinin-4、TFF1、TGFBI 联合预测 PHC 患者 TACE 术后预后的 AUC 为 0.926，敏感度为 81.3%，特异度为 76.8%。**结论**　PHC 患者 TACE 术后预后不良患者血清 actinin-4、TFF1、TGFBI 水平均显著升高，且三者联合测定对患者预后具有良好的预测价值。

关键词： 原发性肝癌；动脉化疗栓塞术；辅肌动蛋白 4；三叶因子 1；转化生长因子 β 诱导蛋白

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Abstract: Objective　To investigate the predictive value of serum actinin-4, trefoil factor 1 (TFF1), and transforming growth factor-β-induced protein (TGFBI) for the prognosis of patients with primary hepatocellular carcinoma (PHC) after transarterial chemoembolization (TACE). **Methods**　From January 2020 to May 2023, 312 patients with PHC who underwent TACE in Shijiazhuang People's Hospital were collected as the study subjects (PHC group), patients with PHC were separated into a group with good prognosis (n=252) and a group with poor prognosis (n=60) based on their postoperative conditions. And 312 subjects who underwent health examinations were selected as the control group. Serum levels of actinin-4, TFF1, and TGFBI were detected by ELISA. Logistic regression was applied to analyze the influencing factors of poor prognosis in patients with PHC after TACE. Receiver operating characteristic curve (ROC) was applied to

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analyze the predictive value of serum actinin-4, TFF1, and TGFBI for poor prognosis after TACE in patients with PHC. **Results** There was no significant difference in gender, age, Child-Pugh grade, and clinical stage between the group with good prognosis and the group with poor prognosis ($P>0.05$), but there were statistically differences in tumor size and portal vein tumor thrombus ($P<0.05$). Compared with control group, the serum levels of actinin-4 [(45.67±10.23) pg/mL *vs* (28.25±6.96) pg/mL, $t=24.868$, $P<0.01$], TFF1 [(5.04±1.53) ng/mL *vs* (2.32±0.64) ng/mL, $t=28.969$, $P<0.01$], TGFBI [(19.16±4.36) ng/mL *vs* (10.25±2.43) ng/mL, $t=31.530$, $P<0.01$] were obviously higher in PHC group. Compared with the group with good prognosis, the serum levels of actinin-4, TFF1, and TGFBI in the group with poor prognosis were obviously increased ($P<0.01$). The results of multivariate logistic regression analysis showed that tumor size, portal vein tumor thrombus, serum actinin-4, TFF1, and TGFBI were all influencing factors for poor prognosis of PHC patients after TACE ($P<0.05$). ROC curve results showed that the combined prediction of serum actinin-4, TFF1, and TGFBI for poor prognosis after TACE in PHC patients had an AUC of 0.926, a sensitivity of 81.3%, and a specificity of 76.8%. **Conclusion** The serum levels of actinin-4, TFF1, and TGFBI in patients with poor prognosis after TACE for PHC are obviously increased, and the combined determination of the three has good predictive value for prognosis of patients.

Keywords: Primary hepatocellular carcinoma; Transarterial chemoembolization; Actinin-4; Trefoil factor 1; Transforming growth factor-β-induced protein

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原发性肝癌(primary hepatocellular carcinoma, PHC)是消化系统常见的恶性肿瘤之一,其早期症状不明显,多数患者在就诊时已为中晚期,错过了手术治疗最佳时机[1]。此时,经导管动脉化疗栓塞术(transarterial chemoembolization, TACE)为 PHC 患者治疗的首选方法,TACE 操作简单,通过栓塞剂阻断肿瘤血供,促使肿瘤组织出现缺血性坏死,以达到治疗目的[2]。然而部分 PHC 患者 TACE 术后出现肿瘤细胞肝内转移或病情复发等不良预后情况[3-4]。因此,有效预测 PHC 患者 TACE 术后预后不良十分必要。辅肌动蛋白 4(actinin-4)作为肌动蛋白绑定蛋白,可参与细胞骨架重建、细胞黏附和形态调节,与肿瘤细胞的侵袭和迁移密切相关[5]。三叶因子 1(trefoil factor 1, TFF1)属于胃黏膜保护因子之一,在胃肠道黏膜损伤修复过程中发挥重要作用,且在多种恶性肿瘤中异常表达[6]。转化生长因子 β 诱导蛋白(transforming growth factor-beta-induced protein, TGFBI)是由转化生长因子 β 诱导分泌的,可促进胃癌细胞发生上皮细胞间质转化,与肿瘤复发转移密切相关[7]。既往研究显示,actinin-4、TFF1、TGFBI 均在胃癌的发生发展中发挥重要作用[5-7],因此,推测三者可能对 PHC 者 TACE 术后预后有一定的预测价值。基于此,本研究对血清 actinin-4、TFF1、TGFBI 在 PHC 者 TACE 术后预后预测中的作用进行探讨,为改善 PHC 患者预后提供参考。

1　资料与方法

1.1　一般资料　选取 2020 年 1 月至 2023 年 5 月在石家庄市人民医院接受 TACE 治疗的 312 例 PHC 患者为研究对象(PHC 组),其中男性 188 例,女性 124 例,年龄 40~72(55.75±6.13)岁。纳入标准:(1) 符合 PHC 相关诊断标准[8],且经肝组织活检确诊;(2) 均符合 TACE 治疗指征;(3) 首次进行 TACE 治疗;(4) Child-Pugh 分级为 A 级或 B 级;(5) 临床分期为Ⅱ~Ⅲ期;(6) 患者临床资料完整。排除标准:(1) 合并其他恶性肿瘤;(2) 既往存在肝脏手术史;(3) 存在肝转移;(4) 免疫功能异常;(5) 介入治疗禁忌;(6) 预计生存时间小于 6 个月。另选取同期在石家庄市人民医院行健康检查者 312 例为对照组,其中男性 182 例,女性 130 例,年龄 40~73(55.25±6.27)岁,PHC 组与对照组在性别、年龄上差异无统计学意义($P>0.05$)。本研究经院伦理委员会审核批准。

1.2　*方法*

1.2.1　血清 actinin-4、TFF1、TGFBI 水平测定　抽取 PHC 患者治疗前及对照组体检当日晨起空腹肘正中静脉血 5 mL,3 500 r/min 离心 15 min 并分离上清,分装于干燥 EP 管中,于-80 ℃下冷藏待测。ELISA 法测定血清 actinin-4、TFF1、TGFBI 水平,使用酶标仪测定不同浓度标准溶液在 450 nm 处吸光度并绘制标准曲线,测定各样本吸光度,并根据标准曲线计算血清 actinin-4、TFF1、TGFBI 水平。actinin-4、TGFBI 试剂盒由上海酶联生物科技提供(批号 ml063245、ml061150),TFF1 试剂盒由 Abcam 公司提供(批号 ab277718)。

1.2.2　短期预后评估　术后 4 周患者复诊时,进行

增强 CT 扫描或 MRI 检查,测量所有目标病灶,并根据实体瘤 RECIST 1.0 评价标准[9]对患者短期预后情况进行评估。(1) 完全缓解:经 TACE 治疗后,靶区实体病灶消失,且维持时间超 4 周;(2) 部分缓解:病灶最大直径之和较基线水平缩小超 30%,且维持超 4 周;(3) 疾病稳定:未出现新病灶,实体病灶直径之和与基线水平相比减少低于 30%,或增加不足 20%;(4) 疾病进展:出现新的病灶或病灶最大直径之和增加超 20%。将完全缓解和部分缓解患者纳为预后良好组(n=252),将疾病稳定和疾病进展患者纳为预后不良组(n=60)。

1.3　统计学方法　SPSS 25.0 统计软件对数据进行处理分析。正态分布的计量资料用 $\bar{x}\pm s$ 表示,采用成组 t 检验;计数资料以例描述,组间比较行 χ^2 检验;多元 logistic 回归分析 PHC 患者 TACE 术后预后不良的影响因素;ROC 曲线分析血清 actinin-4、TFF1、TGFBI 对 PHC 患者 TACE 术后预后不良的预测价值,actinin-4、TFF1、TGFBI 联合与三者独立预测患者预后的 ROC 曲线下面积比较采用 Z 检验。P<0.05 表示差异有统计学意义。

2　结　果

2.1　预后良好组与预后不良组一般资料对比　预后良好组与预后不良组在性别、年龄、Child-Pugh 分级及临床分期上差异无统计学意义(P>0.05)。预后不良组肿瘤≥5 cm 及有门静脉癌栓患者病例数多于预后良好组(P<0.05)。见表 1。

2.2　血清 actinin-4、TFF1、TGFBI 水平对比　与对照组相比,PHC 组患者血清 actinin-4、TFF1、TGFBI 水平均显著升高(P<0.01)。见表 2。预后不良组患者血清 actinin-4、TFF1、TGFBI 水平显著高于预后良好组(P<0.01)。见表 3。

2.3　PHC 患者 TACE 术后预后不良的影响因素 logistic 回归分析　以 PHC 患者 TACE 术后预后状况为因变量(预后不良=1,预后良好=0),以肿瘤大小(<5 cm=0, ≥5 cm=1)、门静脉癌栓(有=1,无=0)、血清 actinin-4、TFF1、TGFBI 水平(均为实测值)为自变量进行多因素 logistic 回归分析。结果显示,肿瘤大小、门静脉癌栓以及血清 actinin-4、TFF1、TGFBI 均为 PHC 患者 TACE 术后预后的影响因素(P<0.05)。见表 4。

2.4　血清 actinin-4、TFF1、TGFBI 对 PHC 患者 TACE 术后预后的预测价值　ROC 曲线结果显示,actinin-4 预测 PHC 患者 TACE 术后预后不良的 AUC 为 0.811(95%*CI*:0.750~0.872),敏感度和特异度分别为 83.3%、62.3%,截断值为 49.98 pg/mL,TFF1 预测 PHC

表 1　预后良好组与预后不良组一般资料对比　(例)

Tab. 1　Comparison of general information between the group with good prognosis and the group with poor prognosis　(case)

指标	预后良好组(n=252)	预后不良组(n=60)	χ^2 值	P 值
性别				
男	148	40	1.275	0.259
女	104	20		
年龄				
<55 岁	134	25	2.568	0.109
≥55 岁	118	35		
Child-Pugh 分级				
A	145	33	0.128	0.721
B	107	27		
肿瘤大小				
<5 cm	154	26	6.275	0.012
≥5 cm	98	34		
临床分期				
Ⅱ期	144	28	2.150	0.143
Ⅲ期	108	32		
门静脉癌栓	113	38	6.636	0.010

表 2　PHC 组与对照组血清 actinin-4、TFF1、TGFBI 水平对比　($\bar{x}\pm s$)

Tab. 2　Comparison of serum actinin-4, TFF1, and TGFBI levels between the PHC group and the control group　($\bar{x}\pm s$)

组别	例数	actinin-4 (pg/mL)	TFF1 (ng/mL)	TGFBI (ng/mL)
对照组	312	28.25±6.96	2.32±0.64	10.25±2.43
PHC 组	312	45.67±10.23	5.04±1.53	19.16±4.36
t 值		24.868	28.969	31.530
P 值		<0.001	<0.001	<0.001

表 3　预后良好组与预后不良组血清 actinin-4、TFF1、TGFBI 水平对比　($\bar{x}\pm s$)

Tab. 3　Comparison of serum actinin-4, TFF1, and TGFBI levels between the group with good prognosis and the group with poor prognosis　($\bar{x}\pm s$)

组别	例数	actinin-4 (pg/mL)	TFF1 (ng/mL)	TGFBI (ng/mL)
预后良好组	252	43.02±10.32	4.62±1.38	18.12±4.15
预后不良组	60	56.81±9.86	6.78±2.15	23.52±5.24
t 值		9.380	9.663	8.586
P 值		<0.001	<0.001	<0.001

表 4　Logistic 回归分析 PHC 患者 TACE 术后预后不良的影响因素

Tab. 4　Logistic regression analysis of factors affecting poor prognosis after TACE in patients with PHC

变量	β	SE	$Wald\chi^2$	P 值	HR	95%CI
肿瘤大小	0.305	0.143	4.557	0.033	1.357	1.025~1.796
门静脉癌栓	0.393	0.155	6.442	0.011	1.482	1.094~2.008
actinin-4	0.551	0.161	11.713	0.001	1.735	1.265~2.379
TFF1	0.490	0.159	9.513	0.002	1.633	1.196~2.230
TGFBI	0.722	0.221	10.665	0.001	2.058	1.335~3.174

患者 TACE 术后预后不良的 AUC 为 0.829(95%*CI*:0.761~0.897),敏感度和特异度分别为 83.3%、65.4%,截断值为 5.92 ng/mL;TGFBI 预测 PHC 患者 TACE 术后预后不良的 AUC 为 0.822(95%*CI*:0.755~0.888),敏感度和特异度分别为 83.3%、63.5%,截断值为 21.48 ng/mL。三者联合预测 PHC 患者 TACE 术后预后不良的 AUC 为 0.926(95%*CI*:0.889~0.963),敏感度为 81.3%,特异度为76.8%;三者联合预测的 AUC 显著大于 actinin-4 单独预测的 AUC($Z=3.162$, $P=0.002$),TFF1 单独诊断的 AUC($Z=2.436$, $P=0.015$),TGFBI 单独诊断的 AUC($Z=2.670$, $P=0.008$)。见图 1。

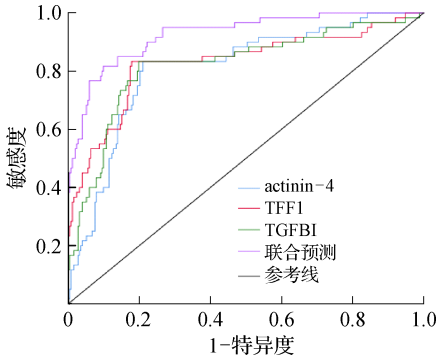

图 1　预测 PHC 患者 TACE 术后预后不良的 ROC 曲线
Fig. 1　ROC curve for predicting poor prognosis after TACE in patients with PHC

3　讨　论

PHC 患者早期无特异性症状,大部分患者在确诊时已为中晚期,错过手术治疗的最佳时机[10]。TACE 是临床中常用的治疗方法,此方法可较好的缩小肿瘤大小,改善患者临床症状,适用于不能切除的中晚期 PHC 患者[11]。然而,TACE 术中产生的缺氧微环境有利于肿瘤细胞生长、促进新血管形成、改变基质降解相关生物活性物质,进而使肿瘤发生复发或转移[12]。目前评估癌症治疗患者预后状况多采用影像学技术,通过观察靶病灶变化情况进而评估患者预后状况,然而此方法受多种干扰因素的影响,且对肿瘤内部血流情况难以显示,无预测价值[13]。

actinin-4 是一种肌动蛋白结合蛋白,也是细胞骨架的组成部分,在 N 端具有肌动蛋白结合域,可与肌动蛋白交联进而维持细胞结构、增强细胞运动[14]。既往研究显示,actinin-4 与肿瘤侵袭、转移密切相关,可作为多种恶性肿瘤的标志物[15]。Fang 等[16]研究显示,乳腺癌患者血清 actinin-4 水平显著高于健康对照组,且对乳腺癌患者临床结局具有良好的预测价值。本研究结果显示,PHC 患者血清 actinin-4 水平显著高于对照组,其水平变化趋势与上述研究结果一致。进一步分析显示,预后不良组患者血清 actinin-4 水平显著高于预后良好组,提示 actinin-4 可能参与 PHC 的发生及恶性进展。分析其原因可能是由于 actinin-4 可促进癌细胞的表型转化及肿瘤细胞的上皮间质转化,增强肿瘤侵袭转移能力;actinin-4 过表达通过与肌动蛋白细胞骨架相互作用,导致肿瘤细胞侵袭、转移能力增加,促进患者不良预后的发生,多因素 logistic 回归分析结果显示,actinin-4 高表达是 PHC 患者预后不良的独立危险因素。

TFF1 是一种主要来源于胃肠道黏膜细胞的小分子多肽,属于三叶因子家族成员之一,既往研究显示,TFF1 在多种恶性肿瘤患者血清或组织中呈高表达,并与肿瘤细胞的增殖、凋亡密切相关,同时参与肿瘤细胞的转移和血管形成[17-18]。胡玉海等[19]研究发现,在乳腺癌患者中,血清 TFF1 水平显著高于健康对照组,且其水平与患者临床分期密切相关。本研究中,PHC 患者血清 TFF1 水平显著高于对照组,且预后不良组显著高于预后良好组,本研究结果与张志峰[20]等在 PHC 患者血清中的研究结果一致,初步提示血清 TFF1 可能参与 PHC 的发生发展。当 TFF1 表达水平升高时,可增加细胞周期蛋白 D1 在细胞中的表达,进而促进细胞增殖、肿瘤的形成,TFF1 还可促进细胞分离和肿瘤血管生成,进而促进肿瘤细胞的浸润转移[17]。此外,高 TFF1 是导致 PHC 患者 TACE 术后预后不良的独立危险因素,这与张志峰[20]等研究结果基本一致。

TGFBI 可直接参与多种临床疾病,如恶性肿瘤、糖尿病、角膜营养不良等[21]。Fico 等[22]研究显示,TGFBI 在乳腺癌患者中呈高表达,且可通过调节乳腺癌肿瘤缺氧机制进而参与到乳腺癌的进展和转移。本研究结果显示,与对照组相比,PHC 患者血清 TGFBI 水平显著升高,且预后不良组患者血清 TGFBI 水平显著高于预后良好组。TGFBI 是一种细胞外基质蛋白,可通过与黏附素结合,使金属蛋白酶被激活,或可促进新生血管形成进而促进肿瘤细胞的侵袭和转移。此外,本研究显示 TGFBI 高表达患者生存预后较差,且血清 TGFBI 是 PHC 患者不良预后的影响因素,提示 TGFBI 可作为 PHC 患者预后判断的肿瘤标志物。ROC 结果显示,血清 actinin-4、TFF1、TGFBI 预测 PHC 患者 TACE 术后预后不良均具有较高的预测效能,且当三者联合检测时,预测价值最高。

综上所述,actinin-4、TFF1、TGFBI 在 PHC TACE 术后预后不良患者血清中均呈高水平,三者对患者预

后不良均具有一定的预测价值,且联合预测价值更高。然而本研究也存在一定的不足,本研究为单中心试验,且未对患者血清 actinin-4、TFF1、TGFBI 水平进行动态监测,未来可实施动态监测并进行前瞻性、多中心试验进一步验证。

利益冲突　无

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