

原发性肝癌患者TACE前后血清GP73动态变化

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摘要: **目的** 评价行肝动脉栓塞化疗术(TACE)的原发性肝癌患者手术前后血清高尔基体蛋白73(GP73)的动态变化及其临床意义;探讨肝癌患者血清GP73与肝功能等指标的相关性,从而找出判断肝癌患者TACE疗效及预后的新血清学标志物。**方法** 应用酶联免疫吸附测定法(ELISA)检测50例行TACE治疗原发性肝癌患者手术前后的血清GP73水平,根据TNM分期、肝脏影像学、甲胎蛋白(AFP)、Child-Pugh分级、PS评分综合评估,将患者分为好转组(23例)和恶化组(27例),观察血清GP73的动态变化与临床转归的关系,并对患者术前血清GP73与肝功能各项指标进行相关性分析,对可能影响GP73水平的临床特征资料进行分析。**结果** 好转组术后1周血清GP73水平较术前明显升高($F = 19.47, P < 0.0001$),术后1~3个月血清GP73较术后1周下降($F = 32.54, P < 0.0001$),且低于术前水平($P = 0.0454$)。恶化组术后1周及术后1~3个月血清GP73较术前均升高($F = 36.71、37.2, P$ 均 < 0.0001),术后1~3个月血清GP73与术后1周无明显变化($P = 0.9111$)。好转组术前及术后1周血清GP73分别与恶化组比较,均无显著差异($P = 0.9693、0.6894$);好转组术后1~3个月血清GP73水平较恶化组明显下降($P = 0.0037$)。两组患者术前血清GP73浓度与AFP水平均无相关性;而与白蛋白(ALB)水平呈负相关,与总胆红素(TBil)、谷氨酰转肽酶(GGT)、天门冬氨酸氨基转移酶(AST)、丙氨酸氨基转移酶(ALT)水平呈正相关;血清GP73水平与是否有淋巴结肿大、是否存在腹水相关(P 均 < 0.05)。**结论** 血清GP73可以作为监测TACE治疗效果的有效指标,血清GP73可以反映肝癌患者肝功能状态。

关键词: 肝肿瘤;放射学;介入性;糖蛋白类

Serum GP73 changes before and after TACE in patients with primary liver cancer

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Abstract: Objective To evaluate the clinical significance of serum GP73 of primary liver cancer patients by observing its dynamic changes and to discuss the relationship between serum GP73 and indexes of the patients' liver function, and to find out the new serological markers which could estimate the prognosis and conventional curative effect of liver cancer patients after transcatheter arterial chemoembolization (TACE). **Methods** ELISA method was applied to detect preoperative and postoperative GP73 levels of 50 cases with primary liver cancer patients treated by TACE. We comprehensively evaluated the patients based on TNM staging, liver imaging, AFP, Child-Pugh grading and PS (performance status) score, and then the patients were divided into worse group (27 cases) and improved group (23 cases). The relationship between dynamic changes of their serum GP73 levels and clinical outcomes was observed. The preoperative serum GP73 levels of the 50 patients with liver cancer and the indicators of their liver functions were observed, and the correlation analysis was carried out. Clinical features that

may affect the GP73 levels were analyzed. **Results** The serum GP73 level of improved group increased obviously one week after the operation ($F = 19.47, P < 0.0001$). One to three months after the operation, the GP73 level decreased compared with that one week after the operation ($F = 32.54, P < 0.0001$) and was lower than the preoperative level ($P = 0.0454$). The serum GP73 level of worse group at one week ($F = 36.7, P < 0.0001$) and one to three months ($F = 37.2, P < 0.0001$) after the operation both increased, and there was no significant change between the serum GP73 level at one to three months and one week after the operation. Comparison between improved and worse group exhibited that there were no statistical differences in serum GP73 level before and one week after the operation. The serum GP73 level of improved group decreased obviously ($P < 0.01$) compared to the worse group one week after operation. The serum GP73 was irrelevant to AFP but was negatively correlated with ALB in 50 patients before operation. There were positive correlations between serum GP73 and TBil, GGT, AST, ALT, respectively. The serum GP73 was related to lymph node enlargement and ascites with P being lower than 0.05. **Conclusions** The serum GP73 could be taken as an effective indicator monitoring the TACE therapeutic effect. It can also reflect the condition of liver function in patients with liver cancer.

Key words: Liver neoplasms; Radiology, interventional; Glycoproteins

经导管肝动脉栓塞化疗术(transcatheter arterial chemoembolization, TACE)是目前治疗中晚期肝癌的首选方法^[1],但对其治疗效果的评价,尚无客观、全面、统一的标准。甲胎蛋白(alpha-fetoprotein, AFP)是目前应用最广泛的原发性肝癌(primary liver cancer, PLC)肿瘤标志物,但在肝癌患者,尤其是对于AFP低浓度及阴性的患者,TACE疗效评估、复发监测等方面尚存在不足。2005年英国学者Block首次报道高尔基体蛋白73(Golgi protein 73, GP73)与原发性肝细胞癌(primary hepatocellular carcinoma, HCC)间密切相关^[2],其后的研究提示GP73在肝癌早期诊断及AFP阴性肝癌的诊断上具有优势^[3],但对于行TACE治疗的肝癌患者,血清GP73的动态变化是否可以反映TACE的治疗效果、监测术后复发,GP73与肝癌患者肝功能是否相关鲜有报道。本研究通过监测行TACE治疗的肝癌患者手术前后GP73的变化及其临床转归,旨在明确血清GP73对于肝癌患者疗效评估、复发监测的意义,从而为临床提供新的更有效的肝癌血清学标志物。

1 资料与方法

1.1 一般资料 选择2012年4月至2013年1月在哈尔滨医科大学附属第四医院感染科及介入科住院的原发性肝癌行TACE的患者50例,所有入组患者均符合卫生部颁布的《原发性肝癌诊疗规范(2011年版)》^[4]对肝癌的诊断标准,并符合《肝癌综合性介入治疗规范化条例(草案)》^[5]对肝癌患者行TACE治疗适应证的

规定。记录患者血清白蛋白(albumin, ALB)、总胆红素(total bilirubin, TBil)、天门冬氨酸氨基转移酶(aspartate aminotransferase, AST)、丙氨酸氨基转移酶(alanine aminotransferase, ALT)、AFP、患者是否有淋巴结肿大、是否存在腹水等相关数据。

1.2 血清标本的采集与分析 所有患者于术前、术后1周、术后1~3个月分别采集静脉血,离心分离血清标本, -80℃冻存备用,同时进行AFP、肝功能等生物化学检测。AFP采用罗氏e601电化学发光法检测,肝功能等生物化学检测应用罗氏C8000进行检测。

1.3 血清GP73检测 采用酶联免疫吸附测定法(enzyme-link immunosorbent assay, ELISA)分别对患者术前、术后1周、术后1~3个月血清行GP73浓度测定,试剂盒为北京热景生物技术公司提供,按照说明书进行操作。

1.4 原发性肝癌TACE术后疗效评估及实验方法 参照2011年卫生部颁布的《原发性肝癌诊疗规范》,在术前及术后1~3个月分别对50例患者进行下列综合评估:①TNM(tumor node metastasis)分期改变;②肝脏CT或核磁共振所示,肿瘤大小有无改变、有无新发病灶;③AFP变化情况;④Child-Pugh分级变化;⑤PS评分的改变。

按照评估结果将患者分为恶化组与好转组。恶化组:TNM分期进展或肿瘤有增大或出现新发病灶或AFP明显升高,Child-Pugh分级恶化、PS(performance status)评分增加。好转组:TNM分期

无进展,肿瘤大小无明显改变且无新发病灶,AFP无明显升高,Child-Pugh分级及PS评分无变化或好转。

分组结果:好转组23例,其中男性18例,女性5例,年龄(57.17 ± 11.54)岁;恶化组27例,其中男性23例,女性4例,年龄(54.67 ± 9.42)岁。分别比较每组及组间术前、术后1周、术后1~3个月血清GP73的变化。将患者术前AFP、肝功能各项指标分别与术前血清GP73进行相关性分析。收集患者临床特征资料:有无淋巴结肿大及腹水、AFP是否大于 $400 \mu\text{g/L}$,并分别与血清GP73进行比较分析;将AFP $< 100 \mu\text{g/L}$ 的患者(20例)进行单独分组,其中术后好转组12例、术后恶化组8例,比较每组及组间术前、术后1周、术后1~3个月血清GP73的变化。

1.5 统计学处理 所有统计学分析均采用SAS 9.1国际标准统计学分析软件进行编程分析,计量资料符合正态分布并采用 $\bar{x} \pm s$ 表示,重复测量的数据采用重复测量的方差分析以及随后的单独效应比较。不符合正态分布采用中位数和四分位数间距表示,相关性分析采用秩相关,组间比较采用秩和检验, $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 患者术前术后血清GP73的变化 好转组术后1周较术前血清GP73水平明显升高,差异有统计学意义($F = 19.47, P < 0.0001$),术后1~3个月血清GP73与术后1周相比有所下降, ($F = 32.54, P < 0.0001$),并低于术前水平($P = 0.0454$),均有统计学意义;恶化组术后1周及术后1~3个月血清GP73较术前均升

高(F 值分别为36.71、37.2, P 均 < 0.0001),术后1~3个月血清GP73水平相对于术后1周无明显变化($P = 0.9111$)。好转组及恶化组比较,术前及术后1周血清GP73差异无统计学意义($P = 0.9693, 0.6894$),好转组术后1~3个月血清GP73水平较恶化组明显下降,差异有统计学意义($P = 0.0037$),见表1。

2.2 肝癌患者血清GP73水平与AFP、ALB、GGT、TbIl的相关性分析 50例患者TACE术前血清GP73与AFP无相关性,秩相关系数(r_s)为0.000768, $P = 0.995775$ 。血清GP73与ALB呈负相关($r_s = -0.5928, P < 0.0001$),与GGT、AST呈高度正相关($r_s = 0.655948, 0.72737, P < 0.0001$),与ALT、TbIl呈正相关($r_s = 0.35456, 0.304558, P < 0.05$),见图1。

2.3 患者血清GP73水平与临床特征资料的分析 患者血清GP73水平与有无淋巴结肿大及腹水有关, $P = 0.0394, 0.0358$;但与患者AFP是否大于 $400 \mu\text{g/L}$ 无相关性, $P = 0.6601$,见表2。

2.4 AFP $< 100 \mu\text{g/L}$ 的肝癌患者TACE手术前后血清GP73的变化 两组患者术前、术后1周与术后1~3个月AFP均无明显改变(P 均 > 0.05),差异无统计学意义;好转组后1~3个月较术前下降($P = 0.028$),恶化组术后1~3个月较术前升高($P = 0.006$),差异均有统计学意义,见图2。

3 讨论

GP73作为新近发现的一个肝癌标志物受到广泛关注,因其在肝癌诊断尤其在AFP阴性肝癌诊断上具有优势被认为是最值得期待的血清标志物之一。目

表 1 好转组及恶化组患者TACE前后GP73变化 ($\bar{x} \pm s, \text{ng/ml}$)

| | 术前 | 术后1周 | 术后1~3个月 |
|------------------|-----------------------|--------------------------|-------------------------|
| 好转组 ($n = 23$) | 170.67 ± 108.85^a | 222.14 ± 122.38^{bc} | 147.36 ± 95.67^{cd} |
| 恶化组 ($n = 27$) | 169.59 ± 89.23 | 234.82 ± 100.48^c | 233.46 ± 102.29^c |

注:与恶化组比较, $^aP = 0.9693$, $^bP = 0.6894$, $^cP = 0.0037$;与术前比较, $P < 0.05$

表 2 血清GP73水平与50例患者临床特征资料的分析

| | | 中位数 | 四分位数间距 | 正态性检验P值 | 秩和检验统计量 | 秩和检验P值 |
|-------------------------|-------------------------|--------|------------------|---------|---------|--------|
| 淋巴结肿大 | 有 ($n = 20$) | 189.58 | (161.96, 285.19) | 0.5167 | 4.2418 | 0.0394 |
| | 无 ($n = 30$) | 114.27 | (80.24, 179.35) | 0.0020 | | |
| 腹水 | 有 ($n = 19$) | 179.35 | (132.49, 291.93) | 0.4989 | 4.4045 | 0.0358 |
| | 无 ($n = 31$) | 121.28 | (71.50, 188.74) | 0.0029 | | |
| AFP ($\mu\text{g/L}$) | < 400 ($n = 28$) | 170.68 | (81.99, 253.72) | 0.0543 | 0.1934 | 0.6601 |
| | ≥ 400 ($n = 22$) | 163.27 | (93.42, 190.42) | 0.0466 | | |

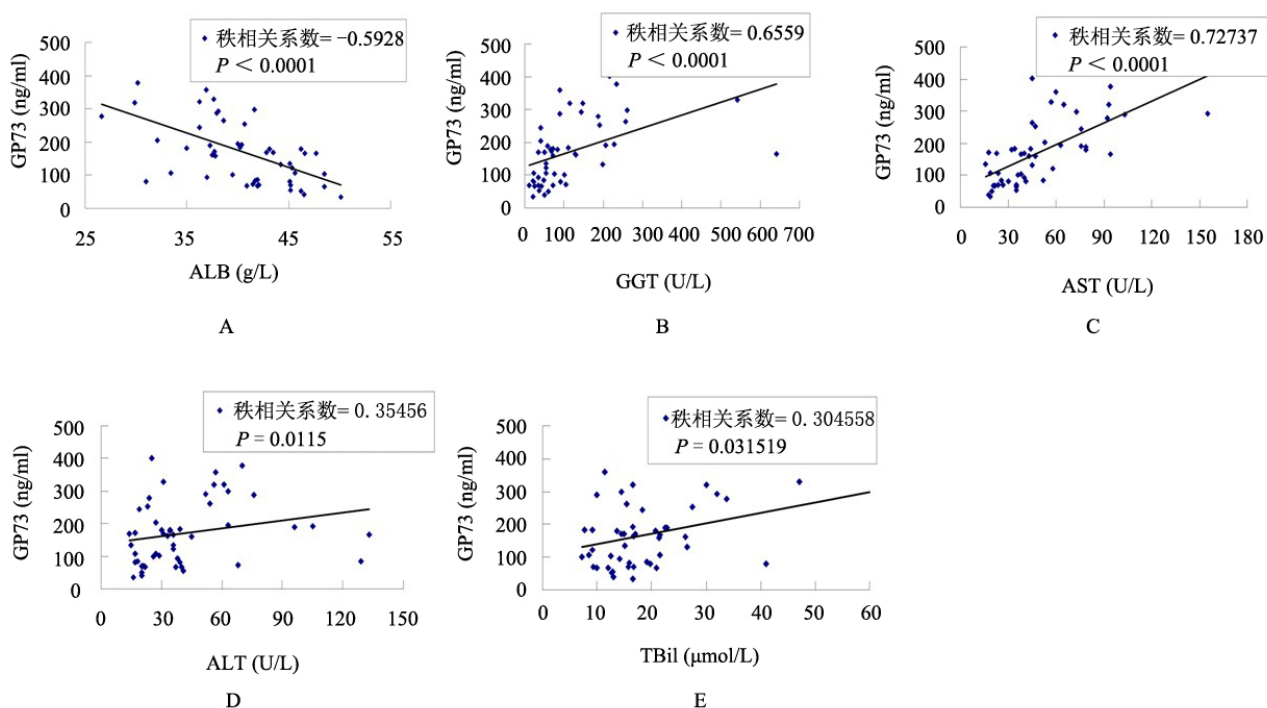
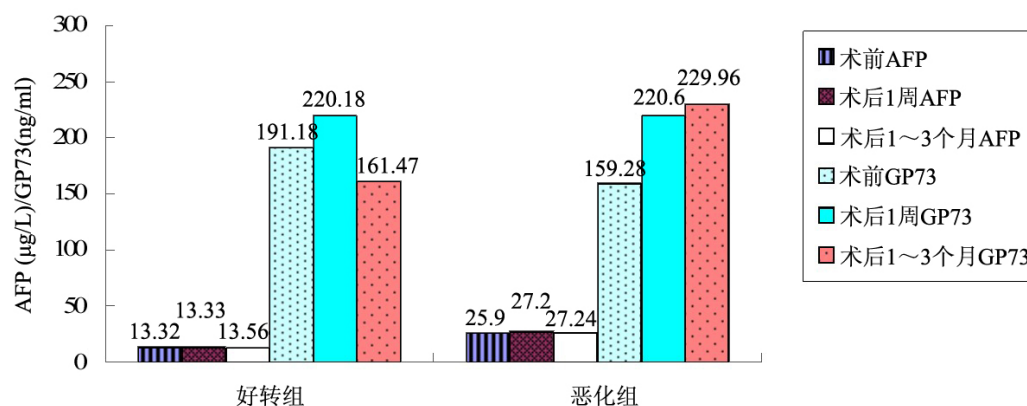


图 1 肝癌患者血清GP73与ALB、GGT、AST、ALT、TBil之间的相关性

图 2 AFP < 100 $\mu\text{g/L}$ 肝癌患者好转组及恶化组TACE前后血清AFP及GP73变化

注: 好转组患者术前AFP水平与术后1周比较无明显改变, $P = 0.993$; 术前AFP水平与术后1~3月比较无明显改变, $P = 0.806$; 术后1周AFP水平与术后1~3月比较无明显改变, $P = 0.849$ 。恶化组患者术前AFP水平与术后1周比较无明显改变, $P = 0.532$; 术前AFP水平与术后1~3月比较无明显改变, $P = 0.742$; 术后1周AFP水平与术后1~3月比较无明显改变, $P = 0.987$ 。好转组患者术前血清GP73水平与术后1周比较无明显改变, $P = 0.054$; 术后1~3月血清GP73水平较术前下降, $P = 0.028$; 术后1~3月血清GP73水平较术后1周明显下降, $P = 0.002$ 。恶化组患者术后1周血清GP73水平较术前明显升高, $P = 0.006$; 术后1~3个月血清GP73水平较术前明显升高, $P = 0.001$; 术后1~3月血清GP73水平较术后1周比较无明显改变, $P = 0.677$ 。

前研究结果显示, 应用免疫印迹法^[3,6,7]检测血清GP73与应用反转录聚合酶链式反应(reverse transcription-polymerase chain reaction, RT-PCR)法^[6,8]分析GP73蛋白表达具有较好的特异性及敏感性, 因此认为其对原发性肝癌的诊断优于AFP, 而应用ELISA方法检测肝硬化及肝癌患者血清中GP73水平报道不尽一致^[9-14], 更缺乏肝癌治疗前后GP73水平动态变化的研究报道。

TACE是目前最常用的治疗中晚期肝癌的方

法, 但对其治疗效果的评价, 尚无客观、全面、统一的标准。本文参照《原发性肝癌诊疗指南》及《肝癌综合性介入治疗规范化条例(草案)》从肿瘤分期、肝脏储备功能、影像学、肿瘤标志物及临床表现综合分析将患者分为好转组及恶化组, 观察每组患者GP73水平的变化与临床转归是否一致, 探索GP73在监测TACE治疗效果及复发检测中的意义。

本研究50例患者术后1周血清GP73较术前均升

高,分析其原因:①TACE栓塞靶血管的同时也会导致正常肝组织缺血缺氧,加之化疗药物对肝脏的损伤,造成人为的急性肝细胞损害,启动了GP73表达上调机制。另外,反复多次治疗可导致或加重肝硬化,肝脏储备能力较差,反复肝纤维化及组织重塑也是慢性肝病患者GP73表达上调的推动力量^[15];②考虑可能与GP73蛋白在血中的降解有关^[16];③患者术前肝脏储备功能、术中肝脏栓塞程度不同、所应用化疗药物的种类剂量不同及个体差异,也是导致GP73浓度高低不一的因素。好转组术后1~3个月血清GP73浓度较术前下降,而恶化组较术前升高,差异均有统计学意义,提示血清GP73的动态变化与肝癌TACE治疗效果相关,血清GP73可作为肝癌疗效评估的指标。值得注意的是,对于AFP阴性及低浓度的患者临床上通过AFP的变化难以反映出TACE治疗的效果,而GP73的动态变化可以准确体现出患者的病情变化,提示对于术前AFP阴性或低于100 μg/L的肝癌患者,血清GP73的动态变化在监测TACE治疗效果方面具有更重要的临床应用价值。

本研究结果显示,肝癌患者血清GP73水平与ALB水平呈负相关,与TBil、GGT、AST及ALT水平呈正相关,笔者推测其与GP73在肝脏中的组织分布及其调节机制有关,随着肝癌细胞生长,正常的肝细胞被破坏且间质细胞增生,而急性肝损害与反复的肝脏组织重塑均可使GP73表达上调^[15]并释放入血,同时肝脏储备功能下降,表现为肝功能恶化。但是否在所有原因导致的肝脏疾病中,GP73均可以反映肝脏功能状态还有待于进一步研究。此外,本研究结果显示患者AFP是否大于400 μg/L与GP73水平无相关性,这与AFP水平与GP73浓度无关的结果一致,而患者出现腹水及淋巴结肿大时GP73水平升高,说明了GP73水平在监测肝癌患者肝脏功能及肿瘤转移方面具有重要意义。

本研究提示血清GP73可以作为监测TACE治疗效果的有效指标,特别是对于AFP阴性及AFP < 100 μg/L的肝癌患者更具重要意义。GP73水平与AFP值变化无相关性,是独立于AFP的新的肿瘤标志物。另外血清GP73水平从另一侧面反映了肝癌

患者的肝功能状态。将GP73与AFP结合起来用于肝癌的诊断及疗效判定将进一步提高肝癌的诊治水平,更大样本的分析研究将为GP73的广泛应用提供更为有利的依据。

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