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AFU, AFP, GP73 和 GPC3 联合检测对原发性肝癌的诊断价值

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摘要 目的:研究α-L- 岩藻糖苷酶(AFU)、甲种胎儿球蛋白(AFP)、高尔基体蛋白 73(GP73)和磷脂酰肌醇蛋白聚糖 3(GPC3)联合检测对原发性肝癌的诊断价值。**方法:**选择 2014 年 1 月～2016 年 5 月在我院进行诊治的原发性肝癌患者 90 例为肝癌组,同期住院诊治的肝硬化患者 60 例为肝硬化组,以及同期在我院体检健康者 60 例为对照组。比较三组的 AFU、AFP、GP73 和 GPC3 水平和阳性检出率,并观察 AFU、AFP、GP73 和 GPC3 单独检测和联合检测对原发性肝癌的诊断效率。**结果:**肝癌组和肝硬化组的 AFU、AFP、GP73 和 GPC3 水平均明显高于对照组(P<0.05),且肝癌组明显高于肝硬化组(P<0.05);肝癌组和肝硬化组的 AFU、AFP、GP73 和 GPC3 阳性率均明显高于对照组(P<0.05),且肝癌组明显高于肝硬化组(P<0.05);AFU、AFP、GP73 和 GPC3 联合检测对原发性肝癌的特异性、敏感性、阳性预测值及阴性预测值均明显高于单独检测和三项指标联合检测 (P < 0.05)。**结论:**AFU、AFP、GP73 和 GPC3 联合检测可以提高对原发性肝癌的检出率,具有较高的临床应用价值。

关键词:α-L- 岩藻糖苷酶;甲种胎儿球蛋白;高尔基体蛋白 73;磷脂酰肌醇蛋白聚糖 3;原发性肝癌

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Value of Combined Detection of AFU, AFP, GP73 and GPC3 in the Diagnosis of Primary Hepatic Carcinoma

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ABSTRACT Objective: To study the value of combined detection ofα-L-fucosidase(AFU), alpha fetoprotein(AFP), Golgi protein 73 (GP73) and glypican 3 (GPC3) in the diagnosis of primary hepatic carcinoma. **Methods:** 90 cases of patients with primary hepatic carcinomawho were treated in our hospital from January 2014 to May 2015were selected as hepatic carcinoma group, 60 cases of patients with liver cirrhosis were selected as liver cirrhosis group, and 20 cases ofhealthy people were selected as control group. The level and positive rate of GPC3, AFP, GP73 and AFU was compared between the three groups, and the diagnostic efficiency of AFU, AFP, GP73 and GPC3 for primary hepatic carcinoma were observed. **Results:** TheAFU, AFP, GP73 and GPC3 level of hepatic carcinoma group and liver cirrhosis group was significantly higher than that of control group (P<0.05), and it was significantly higher in hepatic carcinoma group than that of liver cirrhosis group (P<0.05); the positive rate of AFU, AFP, GP73 and GPC3 of hepatic carcinoma group and liver cirrhosis group was significantly higher than that of control group (P<0.05), and it was significantly higher in hepatic carcinoma group than that of liver cirrhosis group (P<0.05); the specificity, sensitivity, positive predictive value and negative predictive value of AFU, AFP, GP73 and GPC3 combined detection were significantly higher than that of single detection and combined detection (P<0.05). **Conclusions:** The combined detection of AFU, AFP, GP73 and GPC3 can improve the detection rate of primary hepatic carcinoma, and has high clinical application value.

Key words: AFU; AFP; GP73; GPC3; Primary hepatic carcinoma

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前言

原发性肝癌是临床最常见的恶性肿瘤之一,死亡率却仅次于肺癌,具有起病隐匿,进展快、恶性程度极高、预后差的特点[1]。早期诊断原发性肝癌不仅能有效提高患者的手术切除率和术后生存率,还可以改善预后,提高生活质量。目前临床上主要采取超声联合血清 AFP 进行诊断, 但部分肝硬化及慢性肝炎患者也会出现 AFP 升高,AFP 对原发性肝癌的诊断敏感性较低,仅为 45%-65%,因此临床上需要寻找到对原发性肝癌特异度高、敏感性好的诊断指标[2,3]。α-L- 岩藻糖苷酶(AFU)、甲种胎儿球蛋白(AFP)、高尔基体蛋白 73(GP73)和磷脂酰肌醇蛋白聚

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糖 3(GPC3)是临床重要的肿瘤标志物,与肿瘤的发生发展转移和预后密切相关。本研究对肝癌患者、肝硬化患者和健康者的 AFU、AFP、GP73 和 GPC3 进行检测，并对检测结果进行对比分析，以探讨 AFU、AFP、GP73 和 GPC3 四种肿瘤标志物单独及联合检测对原发性肝癌的诊断价值。

1 资料和方法

1.1 一般资料

选择 2014 年 1 月～2016 年 5 月在我院进行诊治的原发性肝癌患者 90 例为肝癌组，均符合原发性肝癌的诊断标准[4]，男 58 例,女 32 例;年龄 26~78 岁,平均(56.12± 12.38)岁。同期住院诊治的肝硬化患者 60 例为肝硬化组，均经 CT 或 B 超检查证实,男 33 例,女 27 例;年龄 25~76 岁,平均(54.37± 11.42)岁。以及同期在我院体检健康者 60 例为对照组，男 32 例,女 28 例;年龄 21~62 岁,平均(51.39± 10.28)岁。本研究获得我院伦理委员会的批准,所有患者均签署知情同意书。三组的年龄和性别分布比较无统计学差异(P>0.05),具有可比性。

1.2 研究方法

肝癌组和肝硬化组患者均于入院次日清晨,对照组于体检当日空腹采集 3 mL 外周血,采用日立 7180 全自动生化分析仪检测 AFU 水平,采用德国罗氏 E170 全自动电化学发光免疫分析仪检测 AFP 水平,采用酶联免疫吸附法检测 GP73、GPC3 水平,试剂盒购自华美生物公司。阳性标准(CUT-OFF 值)为:AFU≥ 35U/L,AFP ≥ 20 μg/L,GP73 ≥ 150 μg/L,GPC3 ≥ 200 ng/L。

1.3 统计学分析

采用 SPSS15.00 软件进行统计学分析，计量资料以 $\bar{x}\pm s$ 表示,组间对比用 t 检验,计数资料用 X^2 检验,以 P<0.05 为差异有统计学意义。

2 结果

2.1 三组 AFU、AFP、GP73 和 GPC3 水平的比较

肝癌组和肝硬化组的 AFU、AFP、GP73 和 GPC3 水平均明显高于对照组(P<0.05),且肝癌组明显高于肝硬化组(P<0.05),见表 1。

表 1 三组 AFU、AFP、GP73 和 GPC3 水平的比较($\bar{x}\pm s$)

Table 1 Comparison of the level of AFU, AFP, GP73 and GPC3 between three groups($\bar{x}\pm s$)

Groups	n	AFU(U/L)	AFP(μg/L)	GP73(μg/L)	GPC3(ng/L)
Liver cancer group	90	72.13± 11.25*#	243.75± 12.96*#	186.43± 42.58*#	3.96± 2.48*#
Liver cirrhosis group	60	16.72± 5.83*	145.28± 11.73*	96.53± 20.35*	1.12± 0.75*
Control group	60	6.95± 3.28	12.36± 3.75	52.13± 16.71	0.53± 0.42

Note: Compared with control group,*P<0.05; compared withliver cirrhosisgroup, #P<0.05.

2.2 三组 AFU、AFP、GP73 和 GPC3 阳性率比较

肝癌组和肝硬化组的 AFU、AFP、GP73 和 GPC3 阳性率均明显高于对照组(P<0.05),且肝癌组明显高于肝硬化组(P<0.05),见表 2。

表 2 三组 AFU、AFP、GP73 和 GPC3 阳性率比较[例(%)]

Table 2 Comparison of the positive rates of AFU, AFP, GP73 and GPC3 between three groups [n(%)]

Groups	n	AFU	AFP	GP73	GPC3
Liver cancer group	90	73(81.11)*#	82(91.11)*#	83(92.22)*#	79(87.78)*#
Liver cirrhosis group	60	7(11.67)*	9(15.00)*	5(8.33)*	4(6.67)*
Control group	60	1(1.67%)	0(0)	0(0)	0(0)

Note: Compared with control group,*P<0.05; compared withliver cirrhosis group, #P<0.05.

2.3 AFU、AFP、GP73 和 GPC3 单独检测和联合检测对原发性肝癌的诊断效率

AFU、AFP、GP73 和 GPC3 联合检测对原发性肝癌诊断的敏感性为 98.08%,特异性为 95.56%,阳性预测值为 98.89 %,阴性预测值为 96.67 %,四者联合检测的特异性、敏感性、阳性预测值及阴性预测值均明显高于任一指标单独检测和三项联合检测的诊断效率 (P < 0.05),见表 3。

3 讨论

原发性肝癌在我国属于高发性癌症，严重威胁着人们的生命健康。目前治疗原发性肝癌最为有效的方法是手术治疗，但对于晚期原发性肝癌患者,手术切除后易发生转移,且复发率高,因此早期诊断原发性肝癌对提高患者生存率、改善生活质量至关重要[5,6]。临床诊断原发性肝癌的方法主要包括肝穿刺活组织检查、影像学检查和化学诊断[7]。组织学检查由于取材通常较少,具有较高的假阴性率,而且取材过程中可能引起肿瘤破裂、出血的发生[8,9]。影像学检查对直径 <2 cm 的良恶性结节和肝癌的鉴别诊断存在一定的局限性,而且检测结果很大程度上取决于检测的仪器设备和操作者的经验水平[10,11]。化学诊断则是选取对原发性肝癌较为敏感的血清肿瘤标志物作为观察指标,进行单独检测或联合检测。

AFU 作为一种分布广泛的溶酶体酸性水解酶，主要功能

表 3 AFU、AFP、GP73 和 GPC3 单独检测和联合检测的诊断效率(%)

Table 3 Diagnostic efficiency of AFU, AFP, GP73 and GPC3 single detection and combined detection(%)

Indexes	Sensibility	Specificity	Positive predictive value	Negative predictive value
AFU	81.11+	93.33+	90.12+	45.74+
AFP	91.11+	92.50+	90.10+	49.58+
GP73	92.22+	95.83+	94.32+	54.10+
GPC3	87.78+	96.67+	95.18+	42.67+
AFU+AFP+GP73	92.31+	89.74+	92.35+	90.36+
AFP+GP73+GPC3	91.52+	90.25+	91.42+	92.45+
AFU+ GP73+GPC3	90.76+	92.31+	93.78+	93.12+
AFU+AFP+GPC3	82.69+	71.76+	90.16+	91.58+
AFU+AFP+GP73+GPC3	98.08	95.56	98.89	96.67

Note: Compared with AFU+AFP+GP73+GPC3 combined detection,+P<0.05.

为分解代谢机体的糖脂蛋白生物活性大分子[12]。当肿瘤细胞出现破裂、坏死时,会释放 AFU 进入血液循环中,使 AFU 水平升高;肝脏出现病变时,肝细胞对 AFU 的清除能力降低,也会升高 AFU 水平[13,14]。原发性肝癌患者的肝癌细胞会产生和分泌大量 AFP 进入到血液循环中,因而血液中 AFP 水平较为稳定并对肝癌的特异性较强,血清 AFP 是临床公认的诊断原发性肝癌的重要方法[15]。GPC3 可以调节细胞分化、增殖、粘附和迁移等,仅在肾脏、肺、卵巢、心脏等少数组织中可见有低水平的表达,而在正常的肝脏组织中未见表达 [16]。血清 GPC3 水平与 AFP 水平无相关性,因此在 AFP 阴性的原发性肝癌的诊断中具有重要作用[17]。GP73 是一种位于高尔基体的跨膜糖蛋白,当肝脏出现病变后,肝脏细胞中 GP73 的表达会发生上调,血清 GP73 水平也随之升高[18,19]。研究发现,GP73 水平的升高可能是由于慢性肝脏组织的纤维化与重构,以及急性肝细胞损伤触发而引起[20]。

近年来,国内外关于 AFU、GP73 和 GPC3 的研究报道逐渐增多,且从单个指标向多个指标联合检测发展,但目前尚未见关于 AFU、AFP、GP73 和 GPC3 联合诊断原发性肝癌的研究。其中 AFP 是最常用的肝癌标志物,但虽然大部分患者血清 AFP 水平升高,仍有一部分患者是阴性或低水平所以单纯依靠极易导致漏诊,AFU GP73 和 GPC3 对肝癌的诊断具有一定的价值,但特异性不高。因此本研究对 AFU、AFP、GP73 和 GPC3 联合检测的诊断价值进行了探讨,以期得出的一种新的诊断模式。结果显示,肝癌组和肝硬化组的 AFU、AFP、GP73 和 GPC3 水平均明显高于对照组(P<0.05),且肝癌组明显高于肝硬化组(P<0.05);肝癌组和肝硬化组的 AFU、AFP、GP73 和 GPC3 阳性率均明显高于对照组(P<0.05),且肝癌组明显高于肝硬化组(P<0.05);提示 AFU、AFP、GP73 和 GPC3 在肝癌患者中的表达水平明显高于肝硬化患者和健康者,可能在肿瘤的发生发展中起重要的作用。AFU、AFP、GP73 和 GPC3 联合检测对原发性肝癌的特异性、敏感性、阳性预测值及阴性预测值均明显高于单独检测和三项联合检测 (P < 0.05)。提示血清肿瘤标志物具有广谱性,单一检测的特异性较低,易遗漏阳性患者,而 AFU、AFP、GP73 和 GPC3 联合检测可互为补充,互为印证,提高原发性肝癌的诊断率。白吉明等[21]将 AFU、AFP 和 GPC3 进行联合检测,结果发现三者联合检测的敏感度为 78.1%,特异度为 66.7%,准确度为 74.1%。与本研究结果基本一致,而四者联合检测诊断的敏感性为 98.08 %,特异性为 95.56 %,阳性预测值为 98.89 %,阴性预测值为 96.67 %,均明显优于三者联合检测。

综上所述,AFU、AFP、GP73 和 GPC3 联合检测可以提高对原发性肝癌的检出率,具有较高的临床应用价值。

参 考 文 献(References)

[1] Molnar C, Silaghi C, Rosca C, et al. Left bisegmentectomy for liver cirrhosis associated primary hepatic carcinoma with preoperative chemoembolization[J]. ActaMedicaMarisiensis, 2014, 60(6): 278-281

[2] Kano Y, Kakinuma S, Goto F, et al. Primary hepatic neuroendocrine carcinoma with a cholangiocellular carcinoma component in one nodule[J]. Clinical Journal of Gastroenterology, 2014, 7(5): 1-6

[3] Chan D L, Alzahrani N A, Morris D L, et al. Systematic review of efficacy and outcomes of salvage liver transplantation after primary hepatic resection for hepatocellular carcinoma [J]. Journal of Gastroenterology &Hepatology, 2014, 29(1): 31-41

[4] Meyer T. Primary liver cancer [J]. British Journal of Cancer, 2013, 108 (4): 995-996

[5] Kano Y, Kakinuma S, Goto F, et al. Primary hepatic neuroendocrine carcinoma with a cholangiocellular carcinoma component in one nodule[J]. Clinical Journal of Gastroenterology, 2014, 7(5): 1-6

[6] Shastri A, Msaouel P, Montagna C, et al. Primary Hepatic Small Cell Carcinoma: Two Case Reports, Molecular Characterization and Pooled Analysis of Known Clinical Data [J]. Anticancer Research, 2016, 36(1): 271-277

[7] Terada T. Primary Small Cell Carcinoma of the Liver: A Case Report with ImmunohistochemicalStudies [J]. Journal of Gastrointestinal Cancer, 2014, 45(S1): 115-119

[8] Lee J W, Kim M W, Choi N K, et al. Double primary hepatic cancer (sarcomatoid carcinoma and hepatocellular carcinoma): A case report [J]. Molecular & Clinical Oncology,2014, 2(6): 949-952

[9] Lepage C, Capocaccia R, Hackl M, et al. Survival in patients with primary liver cancer, gallbladder and extrahepatic biliary tract cancer

and pancreatic cancer in Europe 1999-2007: Results of EUROCARE-5[J]. European Journal of Cancer, 2015, 51(51): 2169-2178

[10] Berentzen T L, Gamborg M, Holst C, et al. Body Mass Index in Childhood and Adult Risk of Primary Liver Cancer [J]. Journal of Hepatology, 2014, 60(2): 325-330

[11] Chen Q W, Cheng C S, Chen H, et al. Effectiveness and complications of ultrasound guided fine needle aspiration for primary liver cancer in a Chinese population with serum α-fetoprotein levels ≤ 200 ng/ml-a study based on 4312 patients[J]. Plos One, 2014, 9(8): e101536-e101536

[12] Mossad N A, Mahmoud E H, Osman E A, et al. Evaluation of squamous cell carcinoma antigen-immunoglobulin M complex (SCCA-IGM) and alpha-l-fucosidase (AFU) as novel diagnostic biomarkers for hepatocellular carcinoma [J]. Tumor Biology,2014,35 (11): 11559-11564

[13] Shen J. Diagnostic significance of combined detection of AFP,AFU, GGT,ALP and CA19-9 in hepatocellular carcinoma [J]. International Journal of Laboratory Medicine, 2012, 6(2): 124-125

[14] Salomon L, Ploussard G, Coloby P, et al. Enquê teobservationnelle, transversale de l'Associationfran aised'urologie (AFU) sur la pratique du traitement hormonal intermittent dans le cancer de la prostate en France[J]. Regresar Al Nú mero, 2014, 24(6): 367-373.

[15] Rojas Y, Guillerman R P, Zhang W, et al. Relapse surveillance in AFP-positive hepatoblastoma: re-evaluating the role of imaging [J]. Pediatric Radiology,2014, 44(10):1275-1280

[16] Rashed H E, Ahmed S A, Hegazy A A, et al. Combined Assessment of EZH2, GPC3 and SUOX could Improve Diagnosis of Regenerative Nodule, Liver Dysplasia and Small HCC in Cirrhotic Patients [J]. International Journal of Advanced Research, 2015, 3(1): 324-346

[17] Luo C, Shibata K, Suzuki S, et al. GPC3 expression in mouse ovarian cancer induces GPC3 specific T cell-mediated immune response through M1 macrophages and suppresses tumor growth [J]. Oncology Reports, 2014, 32(3): 913-921

[18] Wei H, Zhang J, Li H, et al. GP73, a new marker for diagnosing HBV-ACLF in population with chronic HBV infections [J]. Diagnostic Microbiology & Infectious Disease, 2014, 79(1): 19-24

[19] Yang M, Guan Y, Yang Y, et al. Immunological detection of hepatocellular carcinoma biomarker GP73 based on dissolved magnetic nanoparticles[J]. Colloids & Surfaces A Physicochemical & Engineering Aspects, 2014, 443(4): 280-285

[20] Liang R, Chen X Y, Ge L Y, et al. Meta-analysis supports the diagnostic value of GP73 in primary liver cancer [J]. Gastroentế rologie Clinique EtBiologique, 2015, 39(5): e71-e72

[21] 白吉明, 李建华, 钱浩,等. AFP AFU GPC3 联合检测在原发性肝癌诊断中的应用[J]. 河北医学, 2012, 18(4): 496-498
Bai Ji-ming, Li Jian-hua, Qian Yue, et al. Stu du on combined ditection of AFU GPC3 and AFP in the diagnosis of primary liver cancer[J]. Hebei Medicine, 2012, 18(4): 496-498

（上接第 1940 页）

[6] Iyoha O, Abiodun P O. Human rotavirus genotypes causing acute watery diarrhea among under-five children in Benin City, Nigeria[J]. Nigerian journal of clinical practice, 2015, 18(1): 48-51

[7] Mejí a A, Atehortú a S, Fló rez I D, et al. Cost-Effectiveness Analysis of Zinc Supplementation for Treatment of Acute Diarrhea in Children Younger Than 5 Years in Colombia [J]. Journal of pediatric gastroenterology and nutrition, 2015, 60(4): 515-520

[8] Wortel R C, Witte M G, van der Heide U A, et al. Dose-surface maps identifying local dose-effects for acute gastrointestinal toxicity after radiotherapy for prostate cancer [J]. Radiotherapy and Oncology, 2015, 117(3): 515-520

[9] Adugna A, Kibret M, Abera B, et al. Antibiogram of E. coli serotypes isolated from children aged under five with acute diarrhea in Bahir Dar town[J]. African health sciences, 2015, 15(2): 656-664

[10] Zaka-ur-Rab Z, Ahmad S M, Naim M, et al. Effect of short term zinc supplementation on iron status of children with acute diarrhea[J]. The Indian Journal of Pediatrics, 2015, 82(5): 421-426

[11] Chieochansin T, Vutithanachot V, Theamboonlers A, et al. Bufavirus in fecal specimens of patients with and without diarrhea in Thailand [J]. Archives of virology, 2015, 160(7): 1781-1784

[12] Zou T, Mou J, Zhan X. Zinc supplementation in acute diarrhea [J]. The Indian Journal of Pediatrics, 2015, 82(5): 415-420

[13] Lam P W, Bunce P E. A 65-year-old HIV-positive man with acute diarrhea [J]. Canadian Medical Association Journal, 2015, 187(15): 1153-1154

[14] Esona M D, Buteau J, Lucien M A B, et al. Rotavirus Group A Genotypes Detected Through Diarrheal Disease Surveillance in Haiti, 2012 [J]. The American journal of tropical medicine and hygiene, 2015, 93(1): 54-56

[15] Maher G, Pradhan G, Shetty S, et al. Rotavirus infection in children with acute gastroenteritis in Aurangabad, central Maharashtra [J]. Indian pediatrics, 2016, 53(7): 631-633

[16] Ceha H M, Niehe V, Marinelli A W K S, et al. Acute toxicity after a diverting stoma and spacer prior to chemoradiation in lo cally advanced rectal cancer[J]. Radiotherapy and Oncology, 2015, 116(1): 107-111

[17] Saito K, Vielemeyer O. Acute Traveler's Diarrhea: Initial Treatment [J]. Current Treatment Options in Infectious Diseases, 2015, 7 (1): 63-76

[18] Levine A C, Glavis-Bloom J, Modi P, et al. Empirically Derived Dehydration Scoring and Decision Tree Models for Children With Diarrhea: Assessment and Internal Validation in a Prospective Cohort Study in Dhaka, Bangladesh [J]. Global Health: Science and Practice, 2015, 3(3): 405-418

[19] Emamghorashi F, Rajabi S H, Shadman A. Frequency of Rotavirus infection in children with acute gastroenteritis in Jahrom, South of Iran[J]. Iranian Journal of Medical Sciences, 2015, 33(2): 84-87

[20] Patro-Goł ąb B, Shamir R, Szajewska H. Yogurt for treating acute gastroenteritis in children: systematic review and meta-analysis [J]. Clinical Nutrition, 2015, 34(5): 818-824