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血清 CD163、AFU、miR202 在原发性肝癌诊断中的作用及在介入治疗前后的变化 *

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摘要 目的：探讨血清 CD163、α-L- 岩藻糖苷酶（AFU）、微小核糖核酸 202（miR202）在原发性肝癌诊断中的作用及在介入治疗前后的变化。**方法：**选择本院 2018 年 5 月 ~2020 年 6 月收治的 106 例原发性肝癌患者，均予以肝动脉化疗栓塞术（TACE）治疗，同期选择本院收治的 94 例肝硬化患者纳入疾病对照组，门诊健康体检者 113 例纳入健康对照组。对比三组血清 CD163、AFU、miR202，原发性肝癌患者治疗前后 CD163、AFU、miR202。**结果：**原发性肝癌组血清 CD163、AFU 高于疾病对照组及健康对照组，差异有统计学意义（$P<0.05$），miR202 低于对照组及健康对照组（$P<0.05$）；疾病对照组血清 CD163、AFU 高于健康对照组（$P<0.05$），miR202 低于健康对照组（$P<0.05$）。原发性肝癌患者治疗后血清 CD163、AFU 低于治疗前，差异有统计学意义（$P<0.05$）；miR202 高于治疗前，差异有统计学意义（$P<0.05$）。治疗前及治疗后，好转组血清 CD163、AFU 水平均低于无效组，差异有统计学意义（$P<0.05$），miR202 高于无效组，差异有统计学意义（$P<0.05$）；治疗后，好转组血清 CD163、AFU 水平低于治疗前（$P<0.05$），miR202 高于治疗前（$P<0.05$），无效组治疗前后血清 CD163、AFU、miR202 差异无统计学意义（$P>0.05$）。**结论：**血清 CD163、AFU、miR202 能够辅助原发性肝癌的诊断，又可为 TACE 的疗效评价提供参考依据。

关键词：原发性肝癌；诊断；介入治疗；CD1663；α-L- 岩藻糖苷酶；miR202

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Role of Serum CD163, AFU and Mir202 in Diagnosis of Primary Liver Cancer and Their Changes Before and After Interventional Therapy*

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ABSTRACT Objective: To explore the role of serum CD163, α-L- fucosidase (AFU) and MicroRNA 202(miR202) in the diagnosis of primary liver cancer and their changes before and after interventional therapy. **Methods:** 106 patients with primary liver cancer admitted to our hospital from May 2018 to June 2020 were treated by transcatheter arterial chemoembolization (TACE). At the same time, 94 patients with liver cirrhosis admitted to our hospital were selected to be included in the disease control group, and 113 outpatients were included in the healthy control group. Serum CD163, AFU, miR202 were compared among the three groups, and CD163, AFU, miR202 in patients with primary liver cancer before and after treatment. **Results:** Serum CD163 and AFU in primary liver cancer group were higher than those in disease control group and healthy control group ($P<0.05$), and miR202 was lower than those in control group and healthy control group ($P<0.05$); Serum CD163 and AFU in disease control group were higher than those in healthy control group ($P<0.05$), and miR202 was lower than that in healthy control group ($P<0.05$). Serum CD163 and AFU in patients with primary liver cancer after treatment were lower than those before treatment, and the difference was statistically significant ($P<0.05$). miR202 was higher than that before treatment, and the difference was statistically significant ($P<0.05$). Before and after treatment, the levels of serum CD163 and AFU in the improved group were lower than those in the ineffective group ($P<0.05$), and miR202 was higher than that in the ineffective group ($P<0.05$). After treatment, the levels of serum CD163, AFU in improved group were lower than those before treatment ($P<0.05$), and miR202 was higher than that before treatment ($P<0.05$). There was no significant difference in serum CD163, AFU, miR202 in ineffective group before and after treatment ($P>0.05$). **Conclusion:** Serum CD163, AFU and miR202 can assist the diagnosis of primary liver cancer, and can also provide reference for evaluating the curative effect of TACE.

Key words: Primary liver cancer; Diagnosis; Interventional therapy; CD1663; α-L- fucosidase; miR202

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前言

原发性肝癌的发病隐匿、进展快、侵袭能力强，有较高的死亡率，尽早诊治对患者预后改善有积极影响[1]。目前手术切除是其治疗的最有效手段，但调查研究发现[2]，大部分原发性肝癌患者就诊时已合并严重肝硬化或处于晚期，无法进行手术切除。肝癌血供多由肝动脉提供，肝动脉化疗栓塞术（TACE）通过在肝动脉支放置栓塞剂，阻断肿瘤局部血供，致瘤体缺血、坏死，从而缓解患者全身或局部症状，延长患者生存期[3]。但有研究发现[4,5]，TACE 栓塞肿瘤的供血血管后，肿瘤可通过自身代偿作用创建侧支血供，另外肿瘤血供受到限制后可刺激缺氧诱导因子的表达，促进肿瘤进展和癌细胞扩散，导致复发。原发性肝癌的发生发展为多基因、多因素的复杂过程，现有研究发现[6]，CD163 和肿瘤发生发展有直接关系。α-L- 岩藻糖苷酶（AFU）为新型的肿瘤标志物，原发性肝癌患者血清 AFU 水平显著上升[7]。微小核糖核酸（miRNA）能够参与机体系列生物学反应，其异常表达能够导致病理改变。miR202 为其亚型之一，已有研究指出[8]，miR202 能够抑制肿瘤细胞增殖，促进肿瘤细胞凋亡，起到抑癌基因作用。目前有关原发性肝癌患者血清 CD163、AFU、miR202 水平和其在介入治疗前后变化的报道较少，本研究通过观察原发性肝癌患者 TACE 治疗前后血清 CD163、AFU、miR202 的水平，评价其在原发性肝癌诊断中的作用和与介入治疗的相关性，为病情监测和预后评价提供参考依据。

1 资料与方法

1.1 一般资料

选择本院 2018 年 5 月 ~2020 年 6 月收治的 106 例原发性肝癌患者，纳入标准：通过病理组织活检确诊为原发性肝癌；均有 TACE 治疗指征，且治疗前无分子靶向治疗、免疫治疗、放化疗等肿瘤治疗史。排除标准：TACE 治疗禁忌症；预计生存期小于 3 个月。同期选择本院收治的 94 例肝硬化患者纳入疾病对照组，结合影像学、生化指标及临床表现等综合检查确诊为肝硬化，均无肝占位病变。收集本院门诊健康体检者 113 例纳入健康对照组，均无免疫相关疾病、无恶性肿瘤史且无急慢性肝脏疾病。原发性肝癌组年龄 42~72 岁，平均（54.28± 3.96）岁；女 29 例，男 77 例。疾病对照组年龄 39~74 岁，平均（55.03± 3.37）岁；女 23 例，男 71 例。健康对照组年龄 40~73 岁，平均（53.81± 3.57）岁；女 35 例，男 78 例。三组年龄、性别比较无统计学差异（P>0.05）。

1.2 方法

采集原发性肝癌患者 TACE 治疗前 1 d、治疗结束后 1 个月，疾病对照组和健康对照组入院时的外周静脉血，常规分离血清。用酶联免疫吸附法测定受试者血清 CD163 水平，用化学发光法检测 AFU 水平，用实时荧光定量 PCR 检测法测定血清 miR202 表达情况。

1.3 疗效评价

TACE 治疗后 1 个月时进行疗效评价，非典型肝内靶病灶或非靶病灶完全消失，并至少维持 1 个月判定为完全缓解。以治疗前肝内典型靶病灶最长直径之和（SLD）为参考，治疗后靶病灶 SLD 缩小超过 30%，并至少维持 1 个月判定为部分缓解。未达到完全缓解或部分缓解标准，但也未发生进展判定为疾病稳定。以治疗前最小 SLE 为参考，治疗后靶病灶 SLE 增加超过 20%；或者不可测量病灶存在明确进展依据；或者肝内非靶病灶存在明确进展依据；或者有新发肝外病灶发生；或者新发肝内病灶的最长直径超过 1cm 均判定为疾病进展。完全缓解和部分缓解判定为有效；疾病稳定和疾病进展判定为无效[9]。

1.4 统计学分析

数据处理选用 SPSS18.0 软件包，计量资料用（$\bar{x}\pm s$）表示，三组间比较用方差分析，两组间比较选用 t 检验，计数资料用[例（%）]表示，用 x^2 检验比较，P<0.05 表示差异有统计学意义。

2 结果

2.1 各组血清 CD163、AFU、miR202 水平分析

原发性肝癌组血清 CD163、AFU 高于疾病对照组及健康对照组（P<0.05），miR202 低于对照组及健康对照组（P<0.05）；疾病对照组血清 CD163、AFU 高于健康对照组（P<0.05），miR202 低于健康对照组（P<0.05），见表 1。

表 1 各组血清 CD163、AFU、miR202 水平分析（$\bar{x}\pm s$）

Table 1 Analysis of serum levels of CD163, AFU and miR202 in each group（$\bar{x}\pm s$）

Groups	n	CD163（ng/mL）	AFU（U/L）	miR202
Healthy control group	113	296.55± 25.03	12.01± 1.22	1.14± 0.11
Disease control group	94	886.14± 103.27[a]	64.23± 6.94[a]	0.61± 0.06[a]
Primary liver cancer group	106	2018.46± 215.04[ab]	157.88± 17.06[ab]	0.29± 0.03[ab]

Note: VS healthy control group, [a]P<0.05; VS disease control group, [b]P<0.05.

2.2 原发性肝癌治疗前后血清 CD163、AFU、miR202 水平分析

原发性肝癌患者治疗后血清 CD163、AFU 低于治疗前（P<0.05）；miR202 高于治疗前（P<0.05），见表 2。

2.3 原发性肝癌不同疗效者治疗前后血清 CD163、AFU、miR202 水平分析

治疗前及治疗后，好转组血清 CD163、AFU 水平均低于无效组（P<0.05），miR202 高于无效组（P<0.05）；治疗后，好转组血清 CD163、AFU 水平低于治疗前（P<0.05），miR202 高于治疗前（P<0.05），无效组治疗前后血清 CD163、AFU、miR202 比较无统计学差异（P>0.05），见表 3。

3 讨论

原发性肝癌是严重危及机体生命安全的恶性肿瘤，近年来其发生率呈增加趋势，原发性肝癌早期缺乏特异症状，临床就

表 2 原发性肝癌治疗前后血清 CD163、AFU、miR202 水平分析($\bar{x}\pm s$)

Table 2 Analysis of serum CD163, AFU and miR202 levels before and after treatment of primary liver cancer($\bar{x}\pm s$)

Time	n	CD163(ng/mL)	AFU(U/L)	miR202
Before treatment	106	2018.46± 215.04	157.88± 17.06	0.29± 0.03
After treatment	106	1492.43± 147.92[c]	117.03± 13.78[c]	0.61± 0.07[c]

Note: VS before treatment, [c]P<0.05.

表 3 原发性肝癌不同疗效者治疗前后血清 CD163、AFU、miR202 水平分析($\bar{x}\pm s$)

Table 3 Analysis of serum CD163, AFU and miR202 levels in patients with different curative effects of primary liver cancer before and after treatment($\bar{x}\pm s$)

Groups	n	Time	CD163(ng/mL)	AFU(U/L)	miR202
Improved group	64	Before treatment	1758.17± 187.16	134.93± 14.59	0.35± 0.04
		After treatment	900.37± 81.83[c]	71.09± 9.03[c]	0.88± 0.10[c]
Invalid group	42	Before treatment	2415.09± 257.22[d]	192.85± 20.82[d]	0.19± 0.01[d]
		After treatment	2394.11± 248.63	187.02± 21.02	0.19± 0.02

Note: VS improved group, [d]P<0.05; VS the same group before treatment, [c]P<0.05.

诊时大部分患者已处于肝癌晚期[10]。目前研究证实[11,12],晚期原发性肝癌患者的临床获益有限,5 年生存率较低。早期诊治和风险评估对原发性肝癌有重要作用。TACE 为中晚期肝癌患者主要治疗方案,其通过化学和物理途径控制肿瘤生长,既往研究已证实[13,14],TACE 能够一定程度的延长患者生存期。但有研究发现[15],TACE 无法全部杀死瘤组织,有远处转移及复发可能性。目前临床对于 TACE 疗效和预后的判断以影像学检查和血清 AFP 为主,但影像学检查无法准确反映肝占位病变,难以发现 0.3 cm 以下的残余病灶,且不能及时反映癌组织坏死情况,对 TACE 疗效监测的作用有限[16]。AFP 为原发性肝癌的主要肿瘤标志物,目前已广泛用于原发性肝癌诊断和疗效监测,肝细胞恶变时能够刺激 AFP 的大量生成,增加血清 AFP 水平,利于原发性肝癌的诊断[17]。但有研究认为[18],AFP 对肝癌诊断的特异度及灵敏度较低,有假阴性和假阳性可能,且难以准确反映 TACE 的治疗效果。血清学检查的标本易获得,且操作简便,近年来已成为原发性肝癌诊断和疗效监测的重要方式。

既往研究提出[19,20],肿瘤相关巨噬细胞在肿瘤发生发展中有重要作用,其可促进肿瘤侵袭及转移,增加肿瘤进展风险,肿瘤相关巨噬细胞增高对肿瘤不良预后有较高的预测价值。巨噬细胞可分化为 M1 型及 M2 型两种表型,其中 CD163 为 M2 标记产物,其仅在活化的巨噬细胞表面表达,对机体的炎症反应有抑制作用,又可与血红蛋白特异性结合,减轻红细胞溶解所致的毒性[21]。CD163 高表达一方面能够刺激 M2 型巨噬细胞活化,另一方面能够促进肿瘤血管形成,刺激肿瘤生长[22]。相关研究发现[23],血清 CD163 水平和原发性肝癌的恶性肿瘤行为有一定相关性,并指出有远处转移的中晚期肝癌患者血清 CD163 水平较无远处转移者。Miura T 等[24]研究表明,CD163 表达和肿瘤分级增加及生存率降低有关。本研究中,原发性肝癌患者血清 CD163 水平显著上升,与健康组及肝硬化组的 CD163 水平存在明显差异,提示血清 CD163 能够为原发性肝癌的诊断提供理论依据。同时本研究数据显示,TACE 治疗后好转者血清 CD163 水平较无效者低,且好转组与无效组治疗前的 CD163 水平有显著差异,表明治疗前通过观察原发性肝癌患者血清 CD163 水平对疗效有一定预测价值,且随访患者 TACE 治疗后的血清 CD163 水平能够进一步观察患者治疗效果。

AFU 广泛分布于肝、脑、肾等组织中,其可参与机体糖脂及糖蛋白代谢,机体正常状态下其浓度较低[25,26]。肝细胞出现癌变时,可影响肝脏星形细胞对 AFU 残基的识别及消除能力,导致 AFU 在机体蓄积,增加血清中 AFU 水平[27]。另有文献指出[28],肝脏肿瘤细胞能够刺激酶蛋白合成,导致机体血清中 AFU 浓度上升。有研究发现[29],原发性肝癌早期血清 AFU 即可上升,且早于超声诊断。Ishida S 等通过研究发现 [30],AFU 对于 AFP 阴性的原发性肝癌患者有较高的诊断价值。本研究中,原发性肝癌患者血清 AFU 水平较肝硬化及正常对照组高,提示临床通过检测血清 AFU 水平能够利于原发性肝癌的诊断,且本研究原发性肝癌患者血清 AFU 水平较既往报道高,考虑与本研究均为不可切除的原发性肝癌患者,因此疾病程度相对较重有关。近年来又有研究发现[31],AFU 不仅在原发性肝癌诊断中有较高价值,且可用于肝癌进展和术后随访等。本研究结果显示,原发性肝癌经 TACE 治疗后血清 AFU 水平较治疗前降低,但与好转组比较,无效组治疗后血清 AFU 水平相对较高,且与治疗前无显著差异,提示血清 AFU 可作为原发性肝癌患者 TACE 治疗后的随访指标。

miRNA 能够调节靶基因表达,从而参与肿瘤发生发展,有关研究指出[32,33],大部分肿瘤患者 miRNA 表达谱均有一定程度的异常。miR202 存在抑癌基因特性,可抑制多种原癌基因的表达,并抑制细胞增殖,促进细胞凋亡[34]。但目前临床主要通过采集组织标本检测 miRNAs 表达,临床应用有一定限制。最近研究表明[35],miRNA 的表达存在组织特异性,在血清标本中的稳定性较高,不容易在 RNA 酶作用下发生降解。又有研究认为[36]在恶性肿瘤诊断中,血清 miRNA 对肿瘤标志物有一定的补充诊断作用。Tiansheng G 等[37]通过研究发现,前列腺癌患者血清 miR202 表达量显著下降,且和前列腺癌 TNM 分期和分化程度有一定相关性。本研究观察发现,相对于肝硬化,miR202 在原发性肝癌中的表达有所降低,提示血清 miR202 能够用于良恶性肝脏疾病的鉴别诊断,利于原发性肝癌的早期诊断,与[38]文

献报道结果相符。进一步分析发现，TACE 治疗后原发性肝癌患者血清 miR202 表达较治疗前上调，但治疗无效者治疗前后 miR202 则无明显改变，且治疗无效者治疗前血清 miR202 水平又低于好转者，说明血清 miR202 水平对于 TACE 的疗效评估有一定作用。但本研究随访时间较短，未观察血清 CD163、AFU、miR202 与原发性肝癌患者 TACE 治疗后早期生存情况的关系，有待后续研究进一步完善。

综上所述，血清 CD163、AFU、miR202 能够辅助原发性肝癌的诊断，又可为 TACE 的疗效评价提供参考依据。

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