

doi: 10.13241/j.cnki.pmb.2021.01.027

AFP、血流变、超敏 C 反应蛋白检测在早期肝癌诊断价值分析 *

杨静玲¹ 张宁梅^{2Δ} 王凯歌³ 曹婷挺⁴ 张 宁¹

(1 陕西省中医医院检验科 陕西 西安 710003; 2 延安大学附属医院检验科 陕西 延安 716000;

3 西安市西航医院检验科 陕西 西安 710021; 4 渭南市精神病医院检验科 陕西 渭南 714000)

摘要 目的:探讨甲胎蛋白(alphafetoprotein, AFP)、血流变、超敏 C 反应蛋白(hypersensitive C-reactive protein, hs-CRP)等指标检测对早期肝癌患者的诊断价值。**方法:**将我院自 2016 年 5 月至 2019 年 5 月间收治的经手术和病理学检查确诊肝癌患者 115 例作为 A 组, 109 例其他肝脏良性病变患者作为 B 组, 同期体检健康者 98 例作为对照组 C 组, 观察三组对象的 AFP、血流变和超敏 C 反应蛋白等各项指标的水平。**结果:**A 组患者的 AFP 水平和 hs-CRP 水平均明显高于 B 组肝脏良性病变组和 C 组健康对照组, B 组患者 AFP 高于 C 组, 组间差异具有统计学意义($P < 0.05$), B 组和 C 组患者 hs-CRP 水平比较差异无统计学意义($P > 0.05$); A 组患者全血高、中、低切粘度、全血粘度、红细胞压积、血细胞比容、血沉方程 K 值、纤维蛋白原、红细胞聚集指数和红细胞刚性指数等指标水平均明显高于 B 组和 C 组对象, B 组患者血沉和血沉方程 K 值明显高于 C 组, 组间差异具有统计学意义($P < 0.05$); A 组肝癌患者 TNM 分期较高的患者血沉方程 K 值、血细胞比容、血浆粘度和全血低切粘度均明显高于 TNM 低分期的患者, 差异具有统计学意义($P < 0.05$)。**结论:**患者的 AFP、hs-CRP 联合血流变血指标的异常改变可作为鉴别肝脏良性疾病和恶性肿瘤的依据, 同时能提高诊断的准确性, 可在临床范围内推广使用。

关键词:肝癌; 肝脏良性疾病; AFP; 血流变; 超敏 C 反应蛋白; 诊断

中图分类号:R735.7 **文献标识码:**A **文章编号:**1673-6273(2021)01-125-04

Diagnostic Value of AFP, Hemorheology and High-Sensitivity C-reactive Protein in Early Liver Cancer*

YANG Jing-ling¹, ZHANG Ning-mei^{2Δ}, WANG Kai-ge³, CAO Ting-ting⁴, ZHANG Ning¹

(1 Department of Clinical Laboratory, Shaanxi Provincial Hospital of Traditional Chinese Medicine, Xi'an, Shaanxi, 710003, China;

2 Department of Clinical Laboratory, Yan'an University Affiliated Hospital, Yan'an, Shaanxi, 716000, China;

3 Department of Clinical Laboratory, Xi'an West Air Hospital, Xi'an, Shaanxi, 710021, China;

4 Department of Clinical Laboratory, Weinan Psychiatric Hospital, Weinan, Shaanxi, 714000, China)

ABSTRACT Objective: To investigate the diagnostic value of AFP, hemorheology and high-sensitivity C-reactive protein in patients with early liver cancer. **Methods:** A total of 115 patients with liver cancer diagnosed by surgery and pathology from May 2016 to May 2019 were enrolled as group A, 109 patients with benign liver lesions as group B, and 98 patients with physical examination at the same time. In the control group C, the levels of AFP, hemorheology and high-sensitivity C-reactive protein in the three groups were observed. **Results:** The AFP level and hs-CRP level in group A were significantly higher than those in group B and the healthy control group in group C. The AFP in group B was higher than that in group C. The difference between the two groups was statistically significant ($P < 0.05$). There was no significant difference in hs-CRP levels between group B and group C ($P > 0.05$). Group A patients had high blood, medium and low viscosity, whole blood viscosity, hematocrit, hematocrit, and sedimentation equation. The K value, fibrinogen, erythrocyte aggregation index and erythrocyte rigidity index were significantly higher than those in group B and C. The erythrocyte sedimentation rate and erythrocyte sedimentation rate in group B were significantly higher than those in group C. The difference between groups was statistically significant ($P < 0.05$). The blood oxygenation equation K value, hematocrit, plasma viscosity and whole blood low-cut viscosity of patients with high TNM stage in group A were significantly higher than those with low TNM. The difference was statistically significant ($P < 0.05$). **Conclusion:** The abnormal changes of AFP and hs-CRP combined with hemorheology can be used as a basis for the identification of benign liver diseases and malignant tumors. At the same time, the accuracy of diagnosis can be improved and can be promoted and used in clinical practice.

Key words: Liver cancer; Benign liver disease; AFP; Hemorheology; Hypersensitive C-reactive protein; Diagnosis

Chinese Library Classification(CLC): R735.7 **Document code:** A

Article ID: 1673-6273(2021)01-125-04

* 基金项目: 国家自然科学基金项目(81603631)

作者简介: 杨静玲(1988-), 女, 本科, 主管技师, 研究方向: 医学检验, 电话: 15129225358, E-mail: jingjing5358@sohu.com

Δ 通讯作者: 张宁梅(1988-), 女, 本科, 主管检验师, 研究方向: 生物化学与分子生物学, 电话: 15129386550, E-mail: 401163507@qq.com

(收稿日期: 2020-03-26 接受日期: 2020-04-22)

前言

肝癌(liver cancer)具有较高的发病率,是我国高发的,危害极大的恶性肿瘤。患者早期表现不典型^[1,2],确诊的患者多为癌症晚期,失去了手术根治的最佳时机,由此可见,尽早的对患者病情进行准确的诊断是提高肝癌治疗效果的关键^[3,4]。目前临床检查主要依据实验室肿瘤标志物,其中血清 AFP 对诊断肝癌具有一定的特异性^[5],但是单独使用其敏感性和特异性均达不到理想的状态,诸多学者寻求 AFP 联合其他肿瘤标志物检测在确诊肝癌方面的价值^[6,7],患者血流状态的改变,是肝癌细胞经门静脉系统播散,形成微小栓子在肝内播散的重要原因,因此有学者提出血流变化和肿瘤的生长、转移存在一定的关系,此外,非肿瘤标志物 C 反应蛋白在肿瘤诊断的应用也逐渐受到关注^[8,9]。本研究将我院近三年来收治的经手术和病理学检查确诊的肝癌患者 115 例作为研究对象,分析其与肝脏良性疾病患者健康者体内 AFP、血流变学和超敏 C 反应蛋白的水平,旨在探讨三者联合早期诊断肝癌的临床价值。

1 资料与方法

1.1 一般资料

将我院自 2016 年 5 月至 2019 年 5 月间收治的经手术和病理学检查确诊肝癌患者 115 例作为 A 组,109 例其他肝脏良性疾病患者作为 B 组,同期体检健康者 98 例作为对照组 C 组,A 组男 64 例,女 51 例,年龄 34~78 岁,平均年龄 54.81 ± 5.29 岁,TNM 分期 I 期 16 例,II 期 35 例,III 期 43 例,IV 期 21 例;B 组男 60 例,女 49 例,年龄 38~76 岁,平均年龄 56.23 ± 5.36 岁;C 组男 53 例,女 45 例,年龄 35~77 岁,平均年龄 55.87 ± 5.24 岁;三组患者一般资料对比无差异($P > 0.05$)。

1.2 纳入和排除标准

纳入标准:A 组患者经手术、病理学、影像学检查确诊,B

患者疾病为肝硬化、病毒性肝炎、酒精性肝病、肝脓肿等;C 组为体检心、肝、肺、肾功能无异常的健康人群。

排除标准:将合并有心脑血管系统、肺、肾功能障碍、其他脏器或系统良、恶性肿瘤的患者排除。

1.3 方法

于空腹状态下采集三组研究对象的肘静脉血 3 mL,静置 15 min,使用 3000 r/min 离心机离心 10 min,分离得到血清进行如下检测:

hs-CRP:使用罗氏 Cobas8000 全自动生化分析仪,通过免疫比浊法进行检测;AFP^[10]:使用罗氏 E601 电化学发光法和其原装配套试剂和质量控制品进行检测;上述操作严格按照说明书进行操作。

血流变指标^[11,12]:于清晨空腹状态下采集肘静脉血 5 mL 置于含有肝素抗凝剂的试管中,避免血液发生凝集或溶血,使用 BV-100 全自动悬丝式血黏度仪在 37℃ 时测定全血的粘度、血浆粘度、红细胞聚集指数、红细胞刚性指数、血沉方程 K 值;使用 STA 血凝仪,STAGO 公司生产的试剂 Clauss 法测定纤维蛋白原的水平;使用温氏法测红细胞压积,使用 SEDI 全自动血沉仪检测血沉。

1.4 统计学方法

应用 SPSS 21.0,计数资料用(%)表示,组间用 χ^2 检验,计量资料用($\bar{x} \pm s$)表示,组间两两用 t 检验,多重检验用 F 检验, $P < 0.05$ 有统计学意义。

2 结果

2.1 三组 AFP 和 hs-CRP 水平比较

A 组的 AFP 水平和 hs-CRP 水平均明显高于 B 组和 C 组,B 组 AFP 高于 C 组($P < 0.05$),B 组和 C 组 hs-CRP 水平比较差异无统计学意义($P > 0.05$),见表 1。

表 1 三组 AFP 和 hs-CRP 水平比较

Table 1 Comparison of AFP and hs-CRP levels among the three groups

Groups	n	AFP($\mu\text{g/L}$)	hs-CRP(mg/L)
Group A	115	$1178.64 \pm 124.59^{*#}$	$17.38 \pm 5.13^{*#}$
Group B	109	$418.48 \pm 104.92^{*}$	3.82 ± 0.99
Group C	98	5.82 ± 2.10	3.45 ± 0.98

Note: * $P < 0.05$ indicates comparison with group C, # $P < 0.05$ indicates comparison with group B.

2.2 三组血流变指标比较

A 组全血高、中、低切粘度、全血粘度、红细胞压积、血细胞比容、血沉方程 K 值、纤维蛋白原、红细胞聚集指数和红细胞刚性指数等指标水平均明显高于 B 组和 C 组,B 组血沉和血沉方程 K 值明显高于 C 组($P < 0.05$),见表 2。

2.3 不同 TNM 分期肝癌患者血流变指标比较

A 组肝癌患者 TNM 分期较高的患者血沉方程 K 值、血细胞比容、血浆粘度和全血低切粘度均明显高于 TNM 低分期的患者,差异具有统计学意义($P < 0.05$),详见表 3。

3 讨论

肝癌在我国具有较高的发病率,疾病特点为恶性程度高、病情发展快、患者生存期短等,是一类死亡率极高的恶性肿瘤^[13,14]。AFP 是反应肝癌病情变化和评价治疗效果的敏感指标,其水平与肿瘤大小、分化程度密切相关^[15,16],但是部分肝硬化患者也会长期出现 AFP 水平升高,却没有发生肝癌,而约有 20% 的肝癌晚期患者在病故前其 AFP 的水平不超过 10 mg/L^[17,18],因此单独用 AFP 阳性检测肝癌缺乏特异性,因此选择特异性强、敏感度高的检测方法就显得尤为重要^[19,20]。肝癌是一种发病率较高的恶性肿瘤,如果早期筛查高危人群,可以提高患者治愈率,提高生活质量,延迟患者寿命,因此选择具有高特异性、灵敏的指标对于提高早期诊断至关重要。

表 2 三组对象血流变指标比较

Table 2 Comparison of hemorheological indexes of three groups of subjects

Index	A	B	C
High-cut viscosity of whole blood(180mPa·s)	5.36±0.62**	3.41±0.78	3.20±0.84
Whole blood mid-cut viscosity(30mPa·s)	7.04±0.91**	5.33±0.83	5.20±0.88
Low-cut viscosity of whole blood(mPa·s)	17.17±2.56**	14.14±2.40	11.95±2.31
Whole blood viscosity	1.55±0.29**	1.30±0.22	1.29±0.23
Hematocrit (L/L)	0.49±0.14**	0.43±0.15	0.42±0.16
Hematocrit(%)	45.38±7.25**	38.98±7.10*	34.34±6.06
K value of ESR	102.76±21.48**	86.27±23.04*	78.78±26.32
Fibrinogen(g/L)	5.10±1.23**	4.02±0.95	3.95±0.94
Erythrocyte aggregation index	17.61±4.35**	14.07±2.91	13.76±2.87
RBC Rigidity Index	1.21±0.65**	0.820.71	0.75±0.69

Note: * $P < 0.05$ indicates comparison with group C, ** $P < 0.05$ indicates comparison with group B.

表 3 不同 TNM 分期肝癌患者血流变指标比较

Table 3 Comparison of Hemorheological Indexes in Patients with Different TNM Stages of Liver Cancer

TNM staging	n	K value of ESR	Hematocrit (%)	Plasma viscosity(mPa·s)	Low-cut viscosity of whole blood(mPa·s)
Phase I	16	85.73±6.91	38.76±4.63	1.21±0.18	12.65±1.43
Phase II	35	92.31±8.47	43.58±5.14	1.49±0.19	14.02±1.67
Phase III	43	102.73±9.48	49.12±5.97	1.78±0.23	17.98±1.82
Phase IV	21	113.45±11.49	56.13±6.12	1.96±0.26	19.97±1.96

CRP 在正常情况下含量很低,但在受到感染、创伤或炎性疾病时其浓度会上升,其本身并不是肿瘤标志物^[21,22],但是,有资料显示,很多肿瘤患者血清中 CRP 水平呈高表达的状态,分析出现这种情况的主要原因是在肿瘤存在的微环境下,炎症细胞产生的白细胞介素等细胞因子会随着血流到达肝脏,肝细胞在相关细胞因子的诱导下合成 hs-CRP^[23,24],本次研究结果证实这一结论,显示肝癌患者 AFP 和 hs-CRP 水平均明显高于肝脏良性疾病者和健康者。与钊雪鹏^[25]等学者的研究一致,分析发现肝癌组 hs-CRP、AFP 水平均高于良性组和健康组,同时,该学还发现联合检测的可提高诊断灵敏度和准确度。国外学者的研究与本研究略有不同,对 hs-CRP、AFP 水平检测与早期肝癌诊断价值分析研究较少,主要采用正电子发射计算机断层显像(positron emission computed tomography, PET)和 PET/CT 等检测,具有较高敏、准确、特异及定位精确等特点^[26]。本研究在后续还需要分析对比 hs-CRP、AFP 水平检测、PET/CT 检测的价值,从而选择更优的检测方法。

正常的血液流变学能够维持机体血液灌注和代谢,异常会造成机体功能性或器质性障碍^[27,28]。肝癌患者普遍存在血液高凝状态,加之肿瘤细胞释放的促凝因子导致血液凝固性增强^[29]。本次研究结果显示,肝癌患者由于癌细胞改变了红细胞表面电荷,使红细胞聚集性增强,血浆球蛋白和纤维蛋白原的水平也明显增高,促使血沉加快,血沉方程 K 值也明显高于 B 组和 C 组,而纤维蛋白原依附在红细胞表面使其变形力降低,因此肝癌患者的血浆粘度和全血粘度均明显高于其余两组,与此同

时,肝癌患者 TNM 分期较高的患者血流变学指标均明显高于其余两组。与王传新等学者在中国微循环学会第四次全国学术大会的报道类似,该学发现肝癌患者血浆粘度、全血粘度、红细胞压积、血沉、血沉方程 K 值、红细胞聚集性、红细胞刚性指数及纤维蛋白原均显著高于正常对照,说明肝癌患者的血液流变学指标显著增高,分析发生上述情况的原因,可能是红细胞聚集性增高导致血流速度变缓,微循环系统的血液发生淤滞,促进血管内凝血发生,同时血流中的聚集体增多,由于趋肤效应,比聚集体小得多的肿瘤细胞会从血管轴心处向管壁转移,这就在很大程度上增加了肿瘤细胞接触管壁或穿过管壁进入周围组织的机会,这也是肝癌发生转移的一个因素,由此可见,血液流变学指标可解释肝癌患者发生转移的机理,也为诊断和治疗提供了重要的依据。此外,本文可以分析各指标相关关系,通过联合检测以及联合流变学变化指标诊断疾病,可以更好的提高诊断的准确率。本研究通过探究实验室常规指标检测对早期肝癌患者的诊断价值,发现 AFP、hs-CRP 联合血液流变学指标,可以作为鉴别早期肝癌,为疾病的快速诊断提供了检测指标,该方法便捷普遍,准确性高,值得进一步探究应用。但是本研究也存在一定的不足,样本量少,也没有与病理学检测进行检测价值的对比,后续研究中需要进行比较 AFP、hs-CRP 联合血液流变学检测与病理学检测价值的探究。

综上所述,患者的 AFP、hs-CRP 联合血液流变学指标的异常改变可作为鉴别肝脏良性疾病和恶性肿瘤的依据,同时能提高诊断的准确性,可在临床范围内推广使用。

参 考 文 献(References)

- [1] Hou SC, Xiao MB, Run-Zhou NI, et al. Serum GP73 is complementary to AFP and GGT-II for the diagnosis of hepatocellular carcinoma[J]. *Oncology Letters*, 2013, 6(4): 1152-1158
- [2] Badr EAE, Korah TE, Ghani AA, et al. Role of serum glypican-3 in the diagnosis and differentiation of small hepatocellular carcinoma from hepatitis-C virus cirrhosis [J]. *Alexandria Journal of Medicine*, 2014, 50(3): 221-226
- [3] Ma, Liu, Lu, et al. Assessment of high-sensitivity C-reactive protein tests for the diagnosis of hepatocellular carcinoma in patients with hepatitis B-associated liver cirrhosis [J]. *Oncology Letters*, 2017, 13(5): 3457-3464
- [4] Liu X, Ma L, Luo X, et al. Diagnostic value of liver stiffness measurement combined with serum high-sensitivity C-reactive protein detection in HBV-related cirrhosis patients complicated with primary liver cancer[J]. *Zhonghua zhong liu za zhi*, 2015, 37(2): e119
- [5] Han CT, Pei-Jer Chen MD, Carr BI, et al. Phase 2 trial of linifanib (ABT 869) in patients with unresectable or metastatic hepatocellular carcinoma[J]. *Cancer*, 2013, 119(2): 380-387
- [6] Lu J, Zheng L, Li R, et al. Diagnostic value of dynamic monitoring of C-reactive protein in drain drainage to predict early anastomotic leakage after colorectal cancer surgery [J]. *Zhonghua Wei Chang Wai Ke Za Zhi*, 2017, 20(9): 1055-1059
- [7] Wen L, Shin MH, Kang JH, et al. The value of high-sensitivity C-reactive protein in hand and knee radiographic osteoarthritis: data from the Dong-gu Study [J]. *Clinical Rheumatology*, 2018, 37(4): 1099-1106
- [8] Huo JM, Huo R, Hu L, et al. Value of Procalcitonin, High Sensitivity C-reactive Protein and Pancreatic Stone Protein in Predicting Prognosis of Children with Sepsis[J]. *Sichuan da xue xue bao. Yi xue ban*, 2017, 48(3): 422-426
- [9] Nakamura M, Fukukawa T, Kitagawa K, et al. ANNALS EXPRESS: Ten-year standardization of lipids and high-sensitivity C-reactive protein in a randomized controlled trial to assess effects of statins on secondary stroke prevention: Japan Statin Treatment Against Recurrent Stroke (J-STARS)[J]. *Ann Clin Biochem*, 2018, 55(1): 128-135
- [10] Kumari R, Singh H. The prevalence of elevated high-sensitivity C-reactive protein in normal pregnancy and gestational diabetes mellitus[J]. *J Family Med Prim Care*, 2017, 6(2): 259-264
- [11] Patricia C. Valery, Mathieu Laversanne, Paul J. Clark. Projections of primary liver cancer to 2030 in 30 countries worldwide [J]. *Hepatology*, 2017, 67(2): 600-610
- [12] Kalkan RE, Figen Öngöz Dede, Ceren Gökmenoğlu, et al. Salivary fetuin-A, S100A12 and High-Sensitivity C-reactive protein levels in periodontal diseases[J]. *Oral Diseases*, 2018, 24(4): 1554-1561
- [13] Apple FS, Murakami MM, Pearce LA, et al. Multi-Biomarker Risk Stratification of N-Terminal Pro-B-Type Natriuretic Peptide, High-Sensitivity C-Reactive Protein, and Cardiac Troponin T and I in End-Stage Renal Disease for All-Cause Death[J]. *Clinical Chemistry*, 2018, 24(8): 1554-1561
- [14] Liu Y, Chen S, Zheng C, et al. The prognostic value of the preoperative c-reactive protein/albumin ratio in ovarian cancer [J]. *BMC Cancer*, 2017, 17(1): e285
- [15] Deng TB, Zhang J, Zhou YZ, et al. The prognostic value of C-reactive protein to albumin ratio in patients with lung cancer [J]. *Medicine*, 2018, 97(50): e13505
- [16] Golobschwarzl N, Krassnig S, Toeglhofer AM, et al. New liver cancer biomarkers: PI3K/AKT/mTOR pathway members and eukaryotic translation initiation factors [J]. *European Journal of Cancer*, 2018, 56(5): 56-70
- [17] Qiu W, Shi J, Guo L, et al. Medical expenditure for liver cancer in urban China: A 10-year multicenter retrospective survey (2002-2011) [J]. *J Cancer Res Ther*, 2018, 14(9): 163-170
- [18] Sun J, Luo Q, Liu L, et al. Low-level shear stress promotes migration of liver cancer stem cells via the FAK-ERK1/2 signalling pathway[J]. *Cancer Letters*, 2018, 427(12): 1-8
- [19] Ma X, Tan YT, Yang Y, et al. Pre-diagnostic urinary 15-F2t-isoprostane level and liver cancer risk: Results from the Shanghai Women's and Men's Health Studies [J]. *Int J Cancer*, 2018, 143(8): 1896-1903
- [20] Cai M, Sun X, Wang W, et al. Disruption of peroxisome function leads to metabolic stress, mTOR inhibition, and lethality in liver cancer cells[J]. *Cancer letters*, 2018, 225(4): 322-330
- [21] Mazmishvili K, Jayant K, Janikashvili N, et al. Study to evaluate the immunomodulatory effects of radiofrequency ablation compared to surgical resection for liver cancer[J]. *J Cancer*, 2018, 9(17): 3187-3195
- [22] Fang T, Lv H, Lv G, et al. Tumor-derived exosomal miR-1247-3p induces cancer-associated fibroblast activation to foster lung metastasis of liver cancer[J]. *Nat Commun*, 2018, 9(1): e191
- [23] Liu MX, Jin L, Sun SJ, et al. Metabolic reprogramming by PCK1 promotes TCA cataplerosis, oxidative stress and apoptosis in liver cancer cells and suppresses hepatocellular carcinoma [J]. *Oncogene*, 2018, 37(12): 1637-1653
- [24] Zhiyong D. Cinobufacini injection for moderate and advanced primary liver cancer: A systematic review and meta-analysis [J]. *J Chinese Pharmaceutical Sci*, 2019, 28(4): 264-275
- [25] 钞雪鹏, 郑雪. 血清蛋白联合检测鉴别诊断肝癌与肝脏良性疾病的应用价值[J]. *临床医学*, 2017, 37(3): 32-33
- [26] Lanza, Ezio, Donadon, et al. Refining the management of patients with hepatocellular carcinoma integrating 11C-choline PET/CT scan into the multidisciplinary team discussion [J]. *Nucl Med Commun*, 2017, 38(10): 826-836
- [27] Freitas LBRD, Longo L, Santos D, et al. Hepatocellular carcinoma staging systems: Hong Kong liver cancer vs Barcelona clinic liver cancer in a Western population[J]. *World J Hepatol*, 2019, 11(9): 689-700
- [28] Kai He, Xiaolan Yu, Xiaoyan Wang. Baicalein and Ly294002 induces liver cancer cells apoptosis via regulating phosphatidylinositol 3-kinase/Akt signaling pathway [J]. *J Cancer Research & Therapeutics*, 2018, 14(9): e519
- [29] Yuanjie Pang, Christiana Kartsonaki, Iain Turnbull, et al. Diabetes, Plasma Glucose, and Incidence of Fatty Liver, Cirrhosis, and Liver Cancer: A Prospective Study of 0.5 Million People [J]. *Hepatology*, 2018, 68(4): 1308-1318