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生物标志物在肝细胞癌诊断与治疗中的研究进展

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Circulating biomarkers for diagnosis and management of hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is the most common primary liver cancer, but the prognosis of HCC patients is poor due to the difficulty of early diagnosis and high recurrence rate. Therefore, it is particularly important to seek effective methods for early diagnosis and early recurrence monitoring after treatment. Circulating biomarkers play an important role in the diagnosis, progression monitoring, and prognosis evaluation of HCC. In recent years, with the discovery of a variety of new biomarkers, the development of biomarkers-related models, and the emergence of liquid biopsy technology, the diagnosis and treatment of HCC have been greatly improved. This article reviews the latest research advances of biomarkers in the diagnosis and treatment of HCC, aiming to provide new ideas for improving the prognosis of HCC patients.

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Key Words: Hepatocellular carcinoma; Circulating biomarkers; Diagnosis; Prognosis; Liquid biopsy

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摘要

肝细胞癌(hepatocellular carcinoma, HCC)是最常见的原发性肝恶性肿瘤, 但因其早期诊断的困难、复发率较高等特点, 患者预后仍较差. 因此寻求有效的早期

诊断以及治疗后早期复发监测的方法显得尤为重要. 生物标志物在HCC的诊断、进展监测以及预后评估方面都有非常重要的作用, 近年来随着多种新型生物标志物的发现、血清标志物相关模型的构建以及液体活检技术的出现, HCC的诊疗现状得到了极大改善. 本文就近年来生物标志物在HCC的诊断与治疗中的最新研究进展进行综述, 旨在为改善患者的预后提供新思路.

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关键词: 肝细胞癌; 生物标志物; 诊断; 预后; 液体活检

核心提要: 肝细胞癌(hepatocellular carcinoma, HCC)早期诊断困难, 治疗后复发率高, 患者预后较差. 近年来随着各种新型生物标志物的出现, 基于生物标志物构建的数理统计模型的运用, 以及液体活检技术的发展, HCC患者的诊疗现状得到了极大改善.

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0 引言

肝细胞癌(hepatocellular carcinoma, HCC)是最常见的原发性肝恶性肿瘤, 其严重威胁人类的生命和健康, 有文献报道^[1-3], 预计到2030年将会有超过100万人死于HCC. HCC的发病非常隐匿, 早期诊断困难, 超过80%的HCC患者在确诊时就已经处于进展期, 甚至失去手术根治的机会. 早期诊断困难导致患者不能及时得到有效的治疗, 是HCC患者预后较差的主要原因之一^[4,5]. 另外, HCC患者术后5年内的复发率高达70%, 患者在接受根治性治疗后未能对肿瘤进展进行准确监测, 而错过最佳治疗时机, 也是导致HCC患者不良预后的重要原因^[6].

目前多个指南建议对于乙型肝炎病毒感染、肝硬化等HCC发病的高危患者, 采取超声联合甲胎蛋白(alpha-fetoprotein, AFP)的检测进行HCC的早期筛查与诊断, 但其敏感性和特异性并不理想, 且有超过1/3的小肝癌患者存在AFP阴性的情况^[7]. 另外, 近年来非酒精性脂肪性肝硬化相关的HCC患者数量逐年增加, 这一类患者的肝脏脂肪性病变严重, 严重的脂肪性病变大大降低了超声检查对小肝癌诊断的敏感性^[8,9]. 而在HCC患者的治疗后随访过程中, 我们主要采用影像学检查包括超声、增强CT、磁共振等方法联合血清标志物的检测来进行肿瘤治疗后的疗效评价及复发监测, 而这一方法对早期

肿瘤复发的监测敏感性和特异性仍不能令人满意, 且检查繁琐、花费巨大. 因此, 我们亟需找到能提高HCC早期诊断的敏感性及特异性, 以及能在HCC的治疗后随访过程中及时准确地对肿瘤进展进行监测的有效方法, 以便对存在早期复发迹象的患者采取及时有效的治疗干预措施, 从而改善HCC患者的预后.

生物标志物在HCC的诊断、进展监测以及预后评估方面都有非常重要的作用. 近年来, 越来越多的新型生物标志物的出现, 以及一些基于AFP等多个HCC预后相关变量的统计模型的出现, 都极大地改善了HCC的诊疗现状^[10]. 另外, 随着对肝癌细胞研究的深入以及生物学技术的提高, 液体活检技术成为HCC诊断与治疗相关领域的另一个热点. 在此, 本文就近年来生物标志物在HCC的诊断与治疗中的最新研究进展进行综述, 旨在为HCC的早期诊断、治疗后疗效评价、复发监测提供文献及数据支持, 为改善HCC患者的预后提供新思路.

1 血清标志物

1.1 AFP AFP是一种结构与人血清白蛋白类似的生物活性蛋白, 其分子量大约为70 kDa. 1964年Tatarinov首先证实了原发性肝癌患者血清中存在大量AFP, 近几十年来, AFP是最广泛的运用于HCC诊断与预后评估等方面的生物标志物. 但其不管在诊断HCC的敏感性还是特异性方面都不理想. 并且血清AFP值不仅仅只在HCC患者中会升高, 在一些慢性肝病、生殖系统肿瘤患者中同样可能存在AFP的升高, 从而导致AFP诊断HCC的假阳性率上升^[11]. 如果将AFP作为一个独立的筛查指标应用于HCC的诊断显然是不可取的, 但是将AFP与超声检查相结合, 能大大提高对早期HCC的检出率. 近年来一项荟萃分析显示, 超声检查单独用于HCC诊断的敏感性仅为45%, 而将AFP与超声相结合后的敏感性可达到63%^[12]. 此外, AFP在药物疗效预测方面也发挥着重要作用^[13]. 最近一项对565例接受索拉非尼治疗失败的HCC患者的随机对照试验显示, 在AFP水平高的亚组里应用雷莫芦单抗治疗能给患者带来更好的长期预后^[14]. 另外一项来自中国的多中心、大样本的回顾性分析显示, 对于术前AFP>400 ng/mL的HCC患者, 结合其术后AFP水平联合评估可以有效预测肿瘤的复发以及长期预后^[15]. 总之, AFP作为目前在HCC领域运用最广泛的生物标志物, 在HCC的诊断、疗效评估、复发监测等方面都发挥着重要作用. 将AFP与其他检查手段结合, 或者将它与其他指标联合运用于统计模型, 能大大提高AFP在HCC的诊断与治疗方面的价值.

1.2 AFP异质体 AFP异质体是甲胎蛋白异常糖基化的产物. 1970年Purves对HCC患者血清作凝胶电泳时发现

AFP有不同的迁移率, 首先提出了甲胎蛋白异质体这一概念, 随后Taketa等^[16,17]发现原发性肝癌患者血清中AFP与小扁豆素结合后, 电泳分成三带, 并将其依次命名为AFP-L1、AFP-L2、AFP-L3, AFP-L3被认为是诊断早期HCC可靠的生物标志物. 不同研究报道AFP-L3在诊断早期HCC的敏感性范围在49%-60%之间^[18-20], 最近一项来自美国共纳入534例患者的III期独立队列研究表明, 当AFP-L3的截断值为40%时, 其诊断早期HCC的敏感性为40%, 假阳性率为10%^[21]. 总之, 单独应用AFP-L3对HCC的诊断敏感性仍然较低, 但近几年它被纳入多个模型中与其他生物标志物联合应用, 其联合检测的效能得到较大提升. 另外, 有研究表明术前AFP-L3水平有助于监测肝癌术后早期复发, 且术后AFP-L3水平 $\geq 5\%$ 是影响肝癌患者术后较差预后的独立危险因素[风险比(hazard ratio, HR): 1.63, 95%置信区间(95% confidence interval, 95%CI): 1.18-2.26, $P=0.003$]^[22].

1.3 异常凝血酶原 异常凝血酶原, 即维生素K缺乏或拮抗诱导的蛋白-II (protein induced by vitamin K absence or antagonist-II, PIVKA-II), 又称脱- γ -羧基凝血酶原(des- γ -carboxy-prothrombin, DCP), 是一种在肝癌细胞中凝血酶原前体羧化不足产生的蛋白质, 由Liebman等^[23]于1984年首次报道. 有研究表明^[24,25], PIVKA-II对HCC的诊断的灵敏度和特异度分别达到了80%和89%. 在一项对131例早期HCC患者的II期研究中, 单独使用PIVKA-II诊断HCC的曲线下面积(area under the receiver operating characteristic, AUROC)为0.72^[20]. 一项国内的多中心、大样本回顾性研究表明, 使用PIVKA-II单独诊断丙型肝炎相关肝癌(HCV-HCC)以及非酒精性脂肪性肝病相关肝癌(NAFLD-HCC)的AUROC均高于单独使用AFP以及AFP-L3(PIVKA-II 0.90 vs AFP 0.80 vs AFP-L3 0.69; PIVKA-II 0.869 vs AFP 0.76 vs AFP-L3 0.689), 另外, 将PIVKA-II、AFP以及AFP-L3三者联合用于诊断可大大提升其诊断效能^[26,27]. 同时有研究指出PIVKA-II在肝癌细胞的增值、血管浸润和转移过程中发挥着作用, 这意味着它是HCC患者预后判断的潜在标志物^[28,29]. 另有研究表明^[30], 术前PIVKA-II阳性是预测HCC切除术后早期复发的独立危险因素(HR: 2.384, 95%CI: 1.735-3.276, $P<0.001$).

1.4 血清磷脂酰肌醇蛋白聚糖-3 血清磷脂酰肌醇蛋白聚糖-3(glypican-3, GPC3)是一类锚定在细胞膜上的癌胚蛋白, Zhou等^[31]和Anatelli等^[32]在2008年首次报道了其在HCC患者中存在特异性高表达. 近年来, GPC3被认为是一种新的HCC血清标志物, 该蛋白通过激活Wnt信号通路促进肝癌细胞的生长^[33,34]. 虽然有不少研究报道了GPC3用于诊断HCC的敏感度和特异度, 但其结果存在

较大差异, 一项荟萃分析显示其诊断HCC的合并敏感度和合并特异度分别为56%和89%^[35]. 另外, 最新的一项荟萃分析表明, 单独使用GPC3诊断HCC的AUROC为0.7793^[36]. 此外, 近期的一项研究发现GPC3是肝癌患者术后复发的独立危险因素, 并将其联合其他影像学指标纳入术后复发监测的预测模型, 该模型展现出了不错的预测效能(AUROC: 0.931)^[37].

1.5 Dickkopf-1 Dickkopf-1(DKK-1)蛋白属于富含半胱氨酸蛋白家族, 于1998年在非洲蟾蜍胚胎细胞中发现^[38]. 尽管该蛋白被认为是Wnt/ β -catenin信号通路的抑制剂, 但其确切的功能尚未完全阐明^[39,40]. 一项荟萃分析显示^[41], DKK-1诊断HCC的合并敏感度和特异度达到了64%和94%. 另外一项共纳入831名肝癌患者的多中心研究发现^[42], DKK-1在诊断AFP阴性肝癌患者方面的AUROC达到了0.841(95%CI: 0.815-0.923), 并且在诊断早期肝癌患者方面也展现出了不错的效能(AUROC: 0.870, 95%CI: 0.829-0.911). 另有学者研究指出将DKK-1、AFP、PIVKA-II三者联合用于诊断肝癌的AUROC可以达到0.952, 诊断效能优于任何单独与组合的模式^[43]. 对于DKK-1在肝癌的复发监测及预后评估方面的研究较少, 有学者报道DKK-1在评价肝癌患者接受经导管动脉化疗栓塞治疗(transcatheter arterial chemoembolization, TACE)后的疗效中具有一定的预测价值^[44].

2 血清标志物相关模型

AFP作为HCC诊断及肿瘤进展、疗效监测的基础标志物已经是无可争议的, 近年来研究者们以AFP为基础, 将它与多种新型标志物结合纳入统计模型, 可大大提高其敏感度和特异度.

2.1 GALAD模型 GALAD模型是基于性别、年龄、AFP-L3、AFP、DCP这五个变量所构建的统计模型, 用于HCC的早期诊断, 由Johnson等^[45]于2014年首次提出. 该模型在诊断早期HCC的敏感性和特异性分别达到了85.6%和93.3%, AUROC为0.9662, 特别有助于AFP阴性HCC的早期诊断^[45,46]. GALAD模型的计算形式为: $Z = -10.08 + 0.09 \times \text{年龄(岁)} + 1.67 \times \text{性别} + 2.34 \times \log[\text{AFP}(\text{ng/mL})] + 0.04 \times \text{AFP-L3}(\text{ng/mL}) + 1.33 \times \log[\text{DCP}(\text{ng/mL})]$, 其中男性赋值为1, 女性赋值为0. 该模型的效能在一项由梅奥诊所牵头的北美国际队列(一共291名参与者)中得到了独立验证^[46-49]. 然而, 该模型暂缺乏更多大型的前瞻性队列研究来进行检验证明, 目前, 亚洲和中东地区正在进行相关大型前瞻性的队列研究^[50].

2.2 ASAP模型 争对中国乙型肝炎病毒感染相关HCC为主的特点, 2019年在一项国内多中心的前瞻性研究中基于性别、年龄、AFP、DCP四个变量构

建了ASAP模型, 用于HCC的早期诊断^[51]. ASAP模型的计算形式为: $[p/(1-p)] = -7.57711770 + 0.04666357 \times \text{年龄(岁)} - 0.57611693 \times \text{性别} + 0.42243533 \times \ln[\text{AFP}(\text{ng/mL})] + 1.10518910 \times \ln[\text{DCP}(\text{ng/mL})]$, 其中男性赋值为0, 女性赋值为1. 该模型较GALAD模型少了一个变量AFP-L3, 这大大降低了检测成本, 并且针对中国人群, 其用于诊断HCC的效能优于GALAD模型(AUROC: 0.935 *vs* 0.921, $P < 0.006$)^[51]. 另外, 最近的研究显示, ASAP用于诊断早期HCV-HCC的效能同样优于GALAD模型(AUROC: 0.917 *vs* 0.894), 并且在AFP阴性患者亚组中的分析也得到了同样的结论^[52].

2.3 BALAD模型 BALAD模型最初由Toyoda等^[53]于2006年构建, 由胆红素、白蛋白、AFP-L3、AFP、DCP五个变量组成, 现在也称BALAD-2模型, 用于协助评估HCC患者的预后. 该模型的变量由肿瘤负荷(AFP、DCP、AFP-L3)以及肝功能(胆红素、白蛋白)两方面构成, 用于HCC患者预后的评估显然是合理的. 一项来自欧美的多中心研究证明BALAD-2模型可评估不同分级患者的生存率, 另外一项来自日本的纳入24029例HCC患者的全国性调查也发现, BALAD-2模型有助于对肝细胞癌的分期和预后进行评估^[54-56].

2.4 Doylestown算法/Doylestown plus算法 Doylestown算法最初由Wang等^[57]于2016年构建, 该算法模型由log(AFP)、年龄、性别、碱性磷酸酶、丙氨酸氨基转移酶五个指标组成. 随后他们在涉及69例早期HCC(T1或T2期)患者和93例肝硬化对照的II期研究中, 将岩藻糖基化激肽原添加到算法中, 构建Doylestown plus算法, 其诊断早期HCC的AUROC达到了0.97, 分别高于单独使用Doylestown算法和AFP(0.93和0.80)^[58]. 另外在包含29例HCC患者和58例对照组的巢式病例对照研究表明, Doylestown plus算法的敏感性为63.2%^[59]. 目前针对Doylestown plus算法的效能检验有更大的II期队列研究正在进行(NCT03878550)^[60].

3 液体活检

液体活检是指从人体的体液(尤其是血液)中提取具有肿瘤或基因特征信息的微小成分, 主要包括循环游离DNA、循环游离RNA、细胞外囊泡等; 近年来随着对肝癌细胞研究的深入以及生物学技术的提高, 液体活检技术成为HCC诊断与治疗相关领域的另一个热点^[61,62].

3.1 循环游离DNA 循环游离DNA(cell-free DNA, cfDNA)是细胞通过凋亡、坏死和活性分泌释放到包括血液、尿液和脑脊液在内的体液中的DNA分子^[63], 包括循环肿瘤DNA(circulating tumor DNA, ctDNA)、游离线粒体DNA、游离病毒DNA等. 其中, ctDNA主要来源于坏

死的肿瘤细胞, 因此这部分的DNA突变与其来源的肿瘤细胞是相同的, 所以可以通过对其突变基因、甲基化等的检测, 来预测早期肿瘤的发生^[64]. 近年来, ctDNA在HCC的早期诊断以及疗效监测方面的突出表现得到了学者的肯定. 在一项II期病例对照研究中, Chalasani等^[65]构建的一种名为多靶点HCC血液检测(mt-HBT)的算法模型, 将三种甲基化ctDNA标记物、AFP、性别组合纳入模型, 对早期HCC的诊断敏感性为82%, 特异性为87%, AUROC为0.91. Qu等^[66]通过联合检测ctDNA突变(TP53、CTNNB1等)、AFP、PIVKA-II, 对社区中乙肝表面抗原阳性患者进行早期HCC的筛查, 交叉验证显示这个联合检测方法诊断HCC的灵敏度和特异度分别达到了83%和93%. 另外, ctDNA在检测HCC治疗期间或缓解期患者体内残留的癌细胞方面具有一定效能, 从而监测肿瘤早期复发. 一项研究表明^[67], 通过对ctDNA进行相关检测可以在MRI发现复发灶之前预测复发, 其性能似乎优于血清生物标志物AFP、AFP-L3和DCP. 另外一项纳入258例接受肝切除手术的肝癌患者的前瞻性队列研究发现^[68], 术前患者ctDNA中基因突变的总数与肝癌术后的早期复发独立相关($HR = 2.2$, $P < 0.001$), 这表明通过术前对肝癌患者的ctDNA进行相关检测可以预测其术后的早期复发.

除了ctDNA外, 另外一项巢式病例对照研究发现^[69], 游离线粒体DNA含量较低的慢性乙肝患者较含量高的患者发生肝癌的风险更高($OR: 2.21$, $95\%CI: 1.28-3.72$, $P = 0.004$), 这也预示了循环游离线粒体DNA在诊断早期肝癌方面的潜在作用. 此外, 循环游离线粒体DNA还可以用于评价TACE联合中药治疗后的肝癌患者的疗效^[70]. 除此之外, 也有相关研究证实了游离病毒DNA在诊断早期肝癌方面的价值^[71]. 一项观察性研究报道了游离病毒DNA在监测乙肝相关肝癌术后肿瘤残留以及早期复发方面的价值^[72].

3.2 循环游离RNA 循环游离RNA(cell-free RNA, cfRNA)是液体活检另一个获取肿瘤信息的来源, 这是一个非常庞大的家族, 种类繁多, 包括长链非编码RNA(long noncoding RNA, LncRNA)、微小RNAs(microRNAs, miRNAs)、circRNA等. 已有许多研究证实了LncRNA和miRNAs在HCC诊断以及预后判断方面的价值^[73-75]. 有研究表明^[76]LncRNA如LINC00462、HOTAIR和MALAT1, 在肝癌组织中显著上调, 预示其在诊断肝癌方面的潜在作用. 有研究报道^[77], LncRNA在HCC的发生发展过程中起着重要的作用, 在发生转移的HCC患者中LncRNA-ATB上调预示不良的预后; 抑制转移的LncRNA miR503HG上调预示良好的预后. 一项纳入50项研究, 总计3423例肝癌患者和2403例慢性肝病患者的荟萃分析

研究表明^[78], miRNA用于诊断肝癌的AUROC为0.82, 敏感性为75.8%, 特异性为75%。circRNA作为一种共价闭环结构的非编码RNA, 可被分泌到人体循环血液中, 作为疾病诊断的生物标志物^[79]。Zhang等^[80]的研究发现HCC患者血浆中的多种circRNA水平低于肝硬化患者、乙肝患者和健康对照组患者(均 $P<0.001$), 通过ROC分析可以发现其对诊断HCC良好的敏感度和特异度, 并且其在血浆中的水平与TNM分期以及肿瘤大小呈正相关。

3.3 细胞外囊泡 细胞外囊泡(extracellular vesicles, EV)是细胞排出的包含各种生物信息的封闭结构, 可以在人血浆中被检测到, 对细胞外囊泡的分析是液体活检的另一种形式。Sun等^[81]将36例早期HCC患者的血浆与26例肝硬化患者的血浆进行比较, 运用EV芯片对EV进行检测, 以此来诊断HCC的敏感性达到了94.4%, 特异性为88.5%。之后有待更加准确的EV检测芯片的开发以及在更大的队列中对其检测效能进行验证。

4 结论

当前, 由于HCC早期诊断困难以及治疗后较高的复发率, HCC患者的预后仍然较差, 寻求有效的早期诊断以及治疗后早期复发监测的方法显得尤为重要。近年来各种新型生物标志物的出现, 基于各种生物标志物构建的数理统计模型的运用, 以及液体活检技术的出现与推广都大大提高了HCC早期诊断以及复发监测的敏感性与特异性。未来通过对更多新型生物标志物的探索以及更高敏感性与特异度的统计模型的构建, 同时随着二代测序技术的发展, 寻找提高液体活检敏感度的方法并尽可能减少其费用, 以此探索HCC的早期诊断、肿瘤进展、疗效评估、早期复发监测、生存期预测更有效的方法工具, 从而改善HCC患者预后。

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• 消息 •

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本刊讯 本刊采用“顺序编码制”的著录方法,即以文中出现顺序用阿拉伯数字编号排序。提倡对国内同行近年已发表的相关研究论文给予充分的反映,并在文内引用处右上角加方括号注明角码。文中如列作者姓名,则需在“Pang等”的右上角注角码号;若正文中仅引用某文献中的论述,则在该论述的句末右上角注角码号。如马连生^[1]报告……,研究^[2-5]认为……;PCR方法敏感性高^[6,7]。文献序号作正文叙述时,用与正文同号的数字并排,如本实验方法见文献[8]。所引参考文献必须以近2-3年SCIE, PubMed,《中国科技论文统计源期刊》和《中文核心期刊要目总览》收录的学术类期刊为准,通常应只引用与其观点或数据密切相关的国内外期刊中的最新文献,包括世界华人消化杂志(<http://www.wjgnet.com/1009-3079/index.jsp>)和World Journal of Gastroenterology(<http://www.wjgnet.com/1007-9327/index.jsp>)。期刊:序号,作者(列出全体作者)。文题,刊名,年,卷,起页-止页, PMID编号;书籍:序号,作者(列出全部),书名,卷次,版次,出版地,出版社,年,起页-止页。



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