Open Access
DOI:10.3724/zdxbyxb-2023-0483

·meta分析·

血清学标志物甲胎蛋白、PIVKA-Ⅱ和磷脂酰肌醇蛋白聚糖3联合诊断肝癌的meta分析

宋红亮[1,2]，王建国[1,2]，张　会[1,2]，吴勇锋[2]，汪　恺[1,2]，王晓波[2]，徐　骁[2]

1. 浙江中医药大学第四临床医学院，浙江 杭州 310053
2. 浙江省肿瘤融合研究与智能医学重点实验室，浙江 杭州 310003

［摘　要］ **目的：**探讨血清生物标志物甲胎蛋白（AFP）、维生素K缺失或拮抗剂Ⅱ诱导的蛋白质（PIVKA-Ⅱ）和磷脂酰肌醇蛋白聚糖3（GPC-3）单独或联合用于肝细胞癌（以下简称肝癌）诊断的价值。**方法：**检索PubMed、Web of Science、Embase三个数据库，收集2002年以来发表的AFP、PIVKA-Ⅱ和GPC-3单独或联合用于诊断肝癌的文献。根据纳入和排除标准筛选文献并提取相关数据。利用诊断准确性研究的质量评价（QUADAS）检查表对纳入的文献进行质量评价，并采用Meta DiSc软件、Review Manager 5.4软件和Stata 15.1软件对AFP、PIVKA-Ⅱ和GPC-3单用和联合使用诊断肝癌的受试者工作特征曲线下面积（AUC）、敏感度、特异度等指标进行数据分析。**结果：**共纳入32篇文献。Meta分析结果显示，单个标志物用于诊断肝癌时，PIVKA-Ⅱ的AUC值最高，为0.88（95%*CI*：0.85~0.91），其次是GPC-3和AFP；多个标志物联合用于诊断肝癌的AUC均高于单个标志物，其中PIVKA-Ⅱ联合GPC-3诊断的AUC值最高，为0.90（95%*CI*：0.87~0.92）。单个标志物用于诊断肝癌时，PIVKA-Ⅱ和GPC-3的敏感度相对较高（分别为0.75和0.76），但GPC-3的特异度不如PIVKA-Ⅱ和AFP（AFP、PIVKA-Ⅱ和GPC-3分别为0.87、0.88和0.81）；多个标志物联合用于诊断肝癌的敏感度较单个标志物诊断时有所提高，但特异度无明显提高。单个标志物用于诊断肝癌时，PIVKA-Ⅱ的诊断比值比（DOR）最高，为22（95%*CI*：13~36），其次是GPC-3和AFP；两个标志物联合用于诊断肝癌的DOR均高于单个标志物，其中AFP联合GPC-3诊断的DOR最高，为25（95%*CI*：9~67）；三个标志物联合用于诊断肝癌时的DOR明显降低，为10（95%*CI*：7~45）。**结论：**单个标志物用于肝癌诊断时，PIVKA-Ⅱ的诊断价值更高。两种标志物联合能显著提高肝癌诊断的敏感度，三种标志物联合未能进一步提高诊断价值。结合临床实际，推荐AFP联合PIVKA-Ⅱ用于肝癌的诊断。

收稿日期（Received）：2023-10-08　**接受日期（Accepted）：**2024-01-26　**网络预发表日期（Online）：**2024-02-01
基金项目（Funding）：浙江省重点研发计划（2019C03050）

第一作者（First author）：宋红亮，硕士研究生，主要从事肝胆外科疾病诊治研究；E-mail：shl2399@163.com；https://orcid.org/0009-0002-4040-0626

通信作者（Corresponding author）：徐　骁，主任医师，教授，博士生导师，主要从事移植肿瘤学和肝胆胰恶性肿瘤精准诊治、器官修复及移植肝功能研究；E-mail：zjxu@zju.edu.cn；https://orcid.org/0000-0002-2761-2811. 汪　恺，主治医师，硕士生导师，主要从事肝脏损伤修复和再生相关研究；E-mail：kaiw3@zju.edu.cn；https://orcid.org/0000-0003-4152-8752. 王晓波，主治医师，主要从事消化道肿瘤诊治研究；E-mail：wxb2310@163.com；https://orcid.org/0000-0003-2473-9291

[关键词] 肝细胞癌;血清学标志物;甲胎蛋白;维生素K缺失或拮抗剂Ⅱ诱导的蛋白质;磷脂酰肌醇蛋白聚糖3;诊断;meta 分析
[中图分类号] R735.7;R730.43 [文献标志码] A

Combination of serum alpha-fetoprotein, PIVKA-Ⅱ and glypican-3 in diagnosis of hepatocellular carcinoma: a meta-analysis

SONG Hongliang[1,2], WANG Jianguo[1,2], ZHANG Hui[1,2], WU Yongfeng[2], WANG Kai[1,2], WANG Xiaobo[2], XU Xiao[2] (*1. The Fourth Clinical Medical College of Zhejiang Chinese Medical University, Hangzhou 310053, China; 2. Zhejiang Provincial Key Laboratory of Integrated Oncology and Intelligent Medicine, Hangzhou 310003, China*)
Corresponding authors: XU Xiao, E-mail: zjxu@zju.edu.cn, https://orcid.org/0000-0002-2761-2811; WANG Kai, E-mail: kaiw3@zju.edu.cn, https://orcid.org/0000-0003-4152-8752; WANG Xiaobo, E-mail: wxb2310@163.com, https://orcid.org/0000-0003-2473-9291

[**Abstract**] **Objective**: To assess the value of serum alpha-fetoprotein (AFP), protein induced by vitamin K absence or antagonist-Ⅱ (PIVKA-Ⅱ) and glypican-3 (GPC-3) in the diagnosis of hepatocellular carcinoma (HCC). **Methods**: Studies of AFP, PIVKA-Ⅱ, GPC-3 or in combination for the diagnosis of HCC since 2002 were searched in PubMed, Web of Science and Embase databases. The literature was screened according to the inclusion and exclusion criteria, the quality of the included articles was evaluated by QUADAS checklist, and relevant data were extracted by Meta DiSc, Review Manager 5.4 and Stata 15.1. The diagnostic values of AFP, PIVKA-Ⅱ and GPC-3 alone or in combination for HCC were assessed with receiver operating characteristic (ROC) curve. **Results**: A total of 32 articles were included in the study. Meta-analysis showed that when a single marker was used to diagnose HCC, the area under the ROC curve (AUC) of PIVKA-Ⅱ was the highest (0.88, 95%*CI*: 0.85–0.91), followed by GPC-3 and AFP. The AUC of combination of serum markers was higher than that of a single marker, and the AUC of PIVKA-Ⅱ combined with GPC-3 was the highest (0.90, 95%*CI*: 0.87–0.92). When a single marker was used for diagnosis, the sensitivity of PIVKA-Ⅱ and GPC-3 were relatively high (0.75 and 0.76), while the specificity of PIVKA-Ⅱ (0.88) and AFP (0.87) were higher than that of GPC-3 (0.81). The sensitivity of the combination of serum markers was higher than that of a single marker, while the specificity was not significantly improved. When a single marker is used to diagnose HCC, the diagnostic odds ratio (DOR) of PIVKA-Ⅱ was the highest (22, 95%*CI*: 13–36), followed by GPC-3 and AFP. The DOR of the combination of two markers in the diagnosis of HCC was higher than that of a single marker, and the DOR of AFP combined with GPC-3 was the highest (25, 95%*CI*: 9–67). The DOR of the combination of the three markers was significantly reduced to 10 (95%*CI*: 7–45). **Conclusions**: When a single marker is used, PIVKA-Ⅱ has a higher diagnostic value for HCC. The combination of two markers can significantly improve the diagnostic sensitivity, and AFP combined with PIVKA-Ⅱ is recommended for the diagnosis of HCC. The combination of all three markers failed to further improve the diagnostic value.

［**Key words**］ Hepatocellular carcinoma; Serum markers; Alpha-fetoprotein; Protein induced by vitamin K absence or antagonist-Ⅱ; Glypican-3; Diagnosis; Meta-analysis

[J Zhejiang Univ (Med Sci), 2024, 53(1): 131-139.]

［**缩略语**］ 甲胎蛋白(alpha-fetoprotein，AFP)；维生素K缺失或拮抗剂Ⅱ诱导的蛋白质(protein induced by vitamin K absence or antagonist-Ⅱ，PIVKA-Ⅱ)；磷脂酰肌醇蛋白聚糖(glypican，GPC)；受试者工作特征曲线(receiver operating characteristic curve，ROC曲线)；ROC曲线下的面积(area under ROC curve，AUC)；计算机断层扫描(computed tomography，CT)；磁共振成像(magnetic resonance imaging，MRI)；诊断准确性研究的质量评价(Quality Assessment of Diagnostic Accuracy Studies，QUADAS)；酶联免疫吸附法(enzyme linked immunosorbent assay，ELISA)；诊断比值比(diagnostic odds ratio，DOR)；置信区间(confidence interval，CI)；胱天蛋白酶(cysteine aspartic acid specific protease，caspase)

肝细胞癌(以下简称肝癌)是中国60岁以下成年男性病死率最高的肿瘤，且发现时患者往往已是晚期，失去了最佳的手术治疗时机，因此肝癌的早筛早诊至关重要。目前，临床上用于筛查及诊断肝癌的血清学标志物有AFP、PIVKA-Ⅱ和GPC-3等[1]。血清AFP水平是临床上应用最广泛的肝癌血清学标志物[1-2]，但其在妊娠期、慢性活动性肝炎时也可显著升高[3]，且有近50%的肝癌患者AFP水平始终低于常用截断值(20 ng/mL)[4]，加之其敏感性较低，所以在筛查肝癌时需要与超声等影像学检查结合使用。PIVKA-Ⅱ在诊断肝癌时有较高的准确性，但其表达水平与肿瘤大小相关[5]，因此用于诊断早期肝癌存在局限性。研究发现，GPC-3在肝癌患者血清中表达上调[6]，目前已成为诊断肝癌的主要血清标志物之一。但目前有关GPC-3单独用于肝癌诊断的研究结果差异较大，无统一的标准，仍需要进一步研究。目前认为，PIVKA-Ⅱ在单独用于诊断肝癌时的诊断价值高于AFP和GPC-3，且三者间任意两者联用诊断肝癌的准确度均优于单独使用[7-9]。但三种标志物联用是否能进一步提高肝癌诊断的准确度目前尚无定论。本研究拟通过汇总三种标志物单独和联合应用的文献，比较这三种标志物单独或联合应用于肝癌诊断的准确度，以期为肝癌诊断提供参考。

1 材料与方法

1.1 文献检索

检索PubMed、Web of Science和Embase系统中2002年1月1日至2023年8月1日发表的关于AFP、PIVKA-Ⅱ和GPC-3单独或联合诊断肝癌的文献，检索词包括“AFP”“alpha-fetoprotein”“alpha fetoprotein”“PIVKA-Ⅱ”“des-gamma-carboxy-prothrombin”“protein induced by vitamin K absence”“GPC-3”“glypican-3”“glypican 3”“serums”“blood serum”“hepatomas”“hepatocellular carcinoma”“liver cancer”“carcinoma，hepatocellular”“diagnosis”“diagnoses”“diagnoses and examinations”“sensitivity”“specificity”“ROC”“AUC”。检索词根据数据库进行调整，采用MeSH(PubMed)、Emtree(EMBASE)等主题词与自由词相结合的方式。同时，查阅相关文章的参考文献，以发现可能漏掉的研究。

1.2 纳入及排除标准

纳入标准：①临床诊断性实验研究；②肝癌的诊断经组织病理学检查确诊或基于公认指南的影像学(超声、CT或MRI)特征作出判断；③经组织病理学检查确诊或基于公认指南的影像学特征证实的肝癌患者为病例组，非肝癌患者为对照组；④能从文献中完整提取真阳性例数、假阳性例数、假阴性例数和真阴性例数等数据。排除标准：①同时合并其他恶性肿瘤，无法获取单独的肝癌数据；②继发性肝癌患者或采集血样前经历过肝癌的相关治疗；③无法完整提取数据；④动物实验；⑤重复、评论、荟萃分析、会议摘要、病例报告、信件或其他不完整的报告；⑥非诊断性研究；⑦样本来源重复。

由两位研究人员独立按照纳入和排除标准对查找到的文献进行筛选。若遇分歧，则由第三

位研究者决定文献是否纳入研究。

1.3 文献质量评价

利用 Review Manager 5.4 软件使用 QUADAS 检查表评估研究的质量。其中包含专门开发的四大类共 14 个项目,用于评估诊断测试主要研究的质量。每个项目的评分为“是”、“否”或“不清楚”。

1.4 资料提取

从文献中提取第一作者姓名、研究对象的国家/地区、文献发表年份、研究对象数、AFP、PIVKA-Ⅱ及 GPC-3 的检测方法、敏感度、特异度、生物标志物阈值等数据。

1.5 数据分析

利用 Meta Disc 软件和 Stata 15.1 软件进行数据分析,包括阈值效应分析、异质性检验、发表偏倚、汇总敏感度、汇总特异度以及汇总受试者工作特征曲线下面积等。采用敏感度对数与(1—特异度)对数之间的 Spearman 相关系数来判断有无阈值效应。采用 Cochran-Q 检验和 I^2 进行非阈值效应异质性检验。当 I^2 值>50% 时为异质性显著,采用随机效应模型;否则,选择固定效应模型。使用 Deeks 漏斗图评估发表偏倚。

2 结 果

2.1 文献检索结果

共检索到文献 3987 篇,通过筛选及阅读其他文献最终纳入 32 篇文献[10-41]。筛选流程见图 1。

2.2 纳入文献的基本特征

纳入文献的研究人群分布较为广泛,其中以中国人群最多。32 篇研究文献均涉及 AFP 诊断效能研究,25 篇文献对 PIVKA-Ⅱ的诊断效能进行研究,14 篇文献对 GPC-3 的诊断效能进行研究。在标志物的检测方法上,纳入的文献以常用的 ELISA 为主,可以降低因检测方式引起的偏倚。纳入文献中病例组共 3453 例,对照组共 4512 例。纳入文献的基本特征见附表 1。

2.3 纳入研究的质量评价结果

根据 QUADAS 检查表,本次研究纳入的文献均为质量高、偏倚风险低及临床适用性高的文献(图 2 和附图 1)。

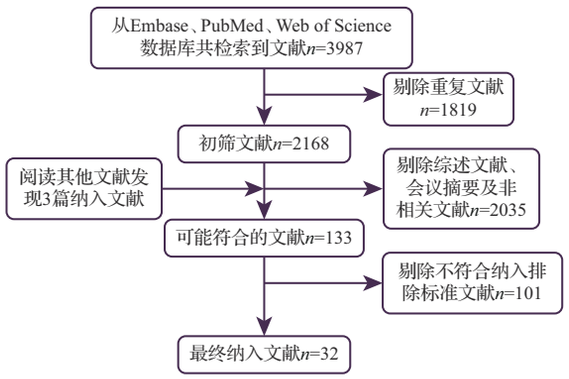

图 1 文献筛选流程图

Figure 1 Literature screening process

2.4 纳入研究异质性检验结果

2.4.1 阈值效应异质性 阈值效应分析结果显示,除 AFP+PIVKA-Ⅱ联合检测存在阈值效应(P<0.05)外,其他检测方式均不存在阈值效应(均 P>0.05),见表 1,提示纳入研究的异质性基本不受阈值效应影响。

2.4.2 非阈值效应异质性 对三种标志物单独或联合使用诊断肝癌的 DOR 进行 Cochran-Q 检验,结果显示 P 值均小于 0.01,表明均存在非阈值效应异质性。除 PIVKA-Ⅱ+GPC-3 的阴性似然比的 I^2 值为 30.3% 外,所有检测方式的敏感度、特异度、阳性似然比、阴性似然比和 DOR 的 I^2 值均大于 50%,表明研究存在较大异质性,遂采用随机效应模型进行以上五个效应量的合并。

2.5 纳入研究发表偏倚检验结果

Deeks 漏斗图显示,AFP、PIVKA-Ⅱ、GPC-3、AFP+PIVKA-Ⅱ、AFP+GPC-3、PIVKA-Ⅱ+GPC-3 和 AFP+PIVKA-Ⅱ+GPC-3 的 P 值均大于 0.05,见图 3。表明研究均不存在发表偏倚。

2.6 meta 分析结果

由于三种标志物单独或联合检测均存在较强异质性,遂采用随机效应模型对来自不同报告的数据进行荟萃分析。

2.6.1 AUC 值 单个标志物用于诊断肝癌时,

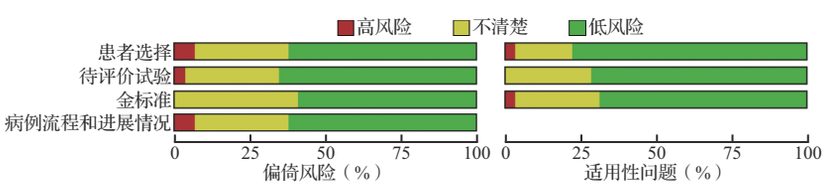

图 2 QUADAS 检查表评价结果

Figure 2 Quality evaluation of the included studies according to QUADAS

表1 阈值效应异质性检验结果

Table 1 The Spearman correlation of markers studied

标志物	Spearman相关系数	*P*值
AFP	0.247	>0.05
PIVKA-Ⅱ	0.061	>0.05
GPC-3	−0.048	>0.05
AFP+PIVKA-Ⅱ	0.513	<0.05
AFP+GPC-3	−0.064	>0.05
PIVKA-Ⅱ+GPC-3	0.400	>0.05
AFP+PIVKA-Ⅱ+GPC-3	0.400	>0.05

AFP：甲胎蛋白；PIVKA-Ⅱ：维生素K缺失或拮抗剂Ⅱ诱导的蛋白质；GPC：磷脂酰肌醇蛋白聚糖.

PIVKA-Ⅱ的AUC值最高，为0.88（95%*CI*：0.85~0.91），其次是GPC-3和AFP。多个标志物联合用于诊断肝癌的AUC均高于单个标志物，其中PIVKA-Ⅱ联合GPC-3诊断的AUC值最高，为0.90（95%*CI*：0.87~0.92）。见表2和附图2。

2.6.2 敏感度和特异度 由于不同AFP研究使用的阈值不同，敏感度和特异度的范围很广，敏感度为28.80%~84.10%，特异度为29.00%~100.00%，汇总后的敏感度和特异度为0.64（95%*CI*：0.60~0.68）和0.87（95%*CI*：0.82~0.91）。单个标志物用于诊断肝癌时，PIVKA-Ⅱ和GPC-3的敏感度相对较高，但GPC-3的特异度不如PIVKA-Ⅱ和AFP；多个标志物联合用于诊断肝癌的敏感度较单个标志物诊断时有所提高，但特异度无明显提高。见表2和附图3。

2.6.3 DOR、阳性似然比和阴性似然比 单个标志物用于诊断肝癌时，PIVKA-Ⅱ的DOR最高，为22（95%*CI*：13~36），其后是GPC-3和AFP；AFP的阳性似然比最高，PIVKA-Ⅱ和GPC-3阴性似然比基本一致，且均低于AFP。两个标志物联合用于诊断肝癌的DOR均高于单个标志物，其中AFP联合GPC-3诊断的DOR最高，为25（95%*CI*：9~67）；AFP联合GPC-3的阳性似然比最高，PIVKA-Ⅱ联合GPC-3的阴性似然比最低。三个标志物联合用于诊断肝癌时的DOR为10（95%*CI*：7~45）。见表2。

综上所述，单个标志物诊断肝癌时PIVKA-Ⅱ的诊断价值最高；两个标志物的联合应用诊断价值优于单个标志物，其中PIVKA-Ⅱ联合GPC-3的诊断价值最高。

3 讨 论

作为发生率和病死率均较高的恶性肿瘤[42]，肝癌的早筛、早诊极为重要。长期以来，血清学标志物AFP因其具有样本易获得、创伤小、可重复等特点已广泛应用于肝癌的筛查和预警[43-45]。1956年，AFP在人胎儿血清中首次发现[46]。从妊娠第四周开始，由于胎儿肝脏等器官的分泌，AFP水平持续升高[47]，待胎儿出生后则持续下降并维持在极低水平，但在肝癌发生时其水平又会异常上升。有研究认为，肝癌患者血清AFP水平升高与位于

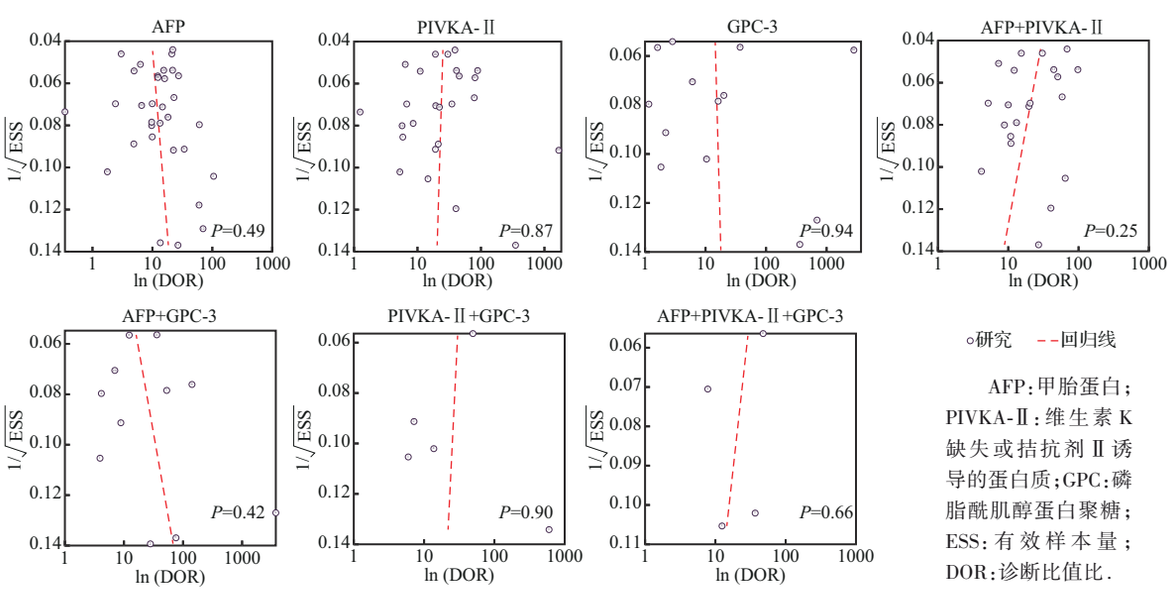

图3 检测文献发表偏倚Deeks漏斗图

Figure 3 Estimation of the publication bias by Deek's funnel plots

表2 三种标志物单独或联合诊断肝癌的合并效应量

Table 2 Diagnostic values of AFP、PIVKA-Ⅱ、GPC-3 and their combinations for hepatocellular carcinoma

标志物	AUC	敏感度	特异度	DOR	阳性似然比	阴性似然比
AFP	0.78(0.74~0.81)	0.64(0.60~0.68)	0.87(0.82~0.91)	12(8~18)	4.9(3.5~6.9)	0.41(0.37~0.46)
PIVKA-Ⅱ	0.88(0.85~0.91)	0.75(0.69~0.80)	0.88(0.83~0.92)	22(13~36)	4.2(4.4~8.9)	0.29(0.23~0.36)
GPC-3	0.84(0.81~0.87)	0.76(0.66~0.84)	0.81(0.66~0.91)	14(4~44)	4.1(2.0~8.3)	0.29(0.18~0.47)
AFP+PIVKA-Ⅱ	0.89(0.85~0.91)	0.79(0.73~0.85)	0.83(0.78~0.88)	19(13~29)	4.8(3.7~6.2)	0.25(0.19~0.32)
AFP+GPC-3	0.89(0.86~0.92)	0.81(0.71~0.88)	0.85(0.73~0.93)	25(9~67)	5.5(2.8~11.0)	0.22(0.14~0.36)
PIVKA-Ⅱ+GPC-3	0.90(0.87~0.92)	0.88(0.78~0.93)	0.74(0.50~0.89)	20(6~68)	3.3(1.5~7.2)	0.17(0.09~0.32)
AFP+PIVKA-Ⅱ+GPC-3	0.80(0.85~0.91)	0.85(0.75~0.92)	0.75(0.45~0.91)	10(7~45)	3.5(1.5~7.9)	0.19(0.13~0.30)

括号中数据为95%置信区间. AFP:甲胎蛋白;PIVKA-Ⅱ:维生素K缺失或拮抗剂Ⅱ诱导的蛋白质;GPC:磷脂酰肌醇蛋白聚糖;AUC:受试者工作特征曲线下面积;DOR:诊断比值比.

人类4号染色体长臂上的相关基因有关,该基因上的独立增强子抑制的阻断和沉默子的缺失导致启动子的活性恢复,最终使得AFP过表达[1, 48]。也有研究证明,AFP可以通过启动环AMP-蛋白激酶A途径、钙离子内流和caspase-3介导的凋亡信号促进肿瘤增殖[49-51]。但是,临床上有约30%的AFP阴性肝癌患者,且其特异度较低,所以目前AFP用于诊断肝癌饱受争议[52]。目前研究显示,PIVKA-Ⅱ诊断肝癌的效能高于AFP,有着较高的敏感度和特异度[5]。PIVKA-Ⅱ可通过增强细胞增殖、肿瘤血管生成等方式促进肿瘤的增殖和转移[53]。目前,PIVKA-Ⅱ在肝癌中过表达的机制尚无定论,肝癌中PIVKA-Ⅱ过表达可能与缺氧微环境、维生素K代谢受损及凝血酶原前体过表达相关。但是,PIVKA-Ⅱ水平不仅在肝癌患者血清中升高,在维生素K缺乏症及服用维生素K拮抗剂患者的血液中也会异常升高,这也使得PIVKA-Ⅱ在诊断肝癌时存在一定局限[54]。GPC-3是GPC家族一员,在正常肝脏组织中几乎不表达,但其在肝癌组织中的阳性率高达90%。其通过Wnt/β-catenin信号通路参与肝癌的发生、增殖和转移,是肝癌的重要血清标志物之一[55]。

为了更好地在临床实践中对肝癌血清标志物进行选择,本研究采取荟萃分析来研究AFP、PIVKA-Ⅱ和GPC-3及其联合在诊断肝癌时的效能。与之前的荟萃分析比较,本研究纳入了更多的近期相关研究,且增加了三个标志物联合(AFP+PIVKA-Ⅱ+GPC-3)的比较。本文资料显示,应用单个标志物诊断肝癌时,PIVKA-Ⅱ的AUC值为0.88,高于AFP的0.78和GPC-3的0.84;在汇总特异度相近的情况下,PIVKA-Ⅱ的汇总敏感度为0.75,明显优于AFP。

从检验诊断学角度来看,PIVKA-Ⅱ的敏感度和诊断准确度最高。然而,单一标志物对于肿瘤的检测往往存在敏感度或特异度的不足,因此需要在单一标志物检测基础上进一步提高肝癌的诊断准确度。分析以往的研究发现,AFP联合PIVKA-Ⅱ诊断肝癌的AUC值多介于0.85~0.90[7, 56-57],而AFP联合GPC-3的AUC值多介于0.75~0.90[58-60],本研究分析结果与其接近,但三种标志物联合应用并未进一步提高诊断准确度。综合之前的一些荟萃分析结果,本研究认为在临床上使用两个标志物的联合可以在一定程度上增加诊断效能。虽然本文资料显示PIVKA-Ⅱ联合GPC-3的AUC值最高,但相比AFP联合PIVKA-Ⅱ提高较少,同时AFP早已广泛应用于临床,而GPC-3的临床应用很少,再加上其高昂的检测价格,难以在临床推广应用。综合上述考虑,本研究建议临床诊断肝癌时可以联合应用AFP和PIVKA-Ⅱ这两个指标,PIVKA-Ⅱ可以降低对AFP阴性肝癌患者漏诊的可能,AFP可以减少对维生素K缺乏及服用维生素K拮抗剂患者的误诊。

但是,本研究仍有一定的局限性。首先,纳入的GPC-3相关研究较少,可能会使GPC-3相关结果存在误差。其次,纳入的都是回顾性研究,且有个别研究是在肝癌高危人群中进行的,使得研究资料存在异质性。因此,本研究结果还需要通过临床试验进一步验证。

本文附表和附图见电子版。

志谢 研究得到浙江省重点研发计划（2019C03050）支持

Acknowledgements This work was supported by the Key R&D Plan of Zhejiang Province (2019C03050)

利益冲突 所有作者均声明不存在利益冲突

Conflict of Interests The authors declare that there is no conflict of interests

参考文献（References）

[1] HU X, CHEN R, WEI Q, et al. The landscape of alpha fetoprotein in hepatocellular carcinoma: where are we?[J]. **Int J Biol Sci**, 2022, 18(2): 536-551.

[2] TERENTIEV A A, MOLDOGAZIEVA N T. Alpha-fetoprotein: a renaissance[J]. **Tumour Biol**, 2013, 34(4): 2075-2091.

[3] TOMASI T B J R. Structure and function of alpha-fetoprotein[J]. **Annu Rev Med**, 1977, 28: 453-465.

[4] FARINATI F, MARINO D, DE GIORGIO M, et al. Diagnostic and prognostic role of alpha-fetoprotein in hepatocellular carcinoma: both or neither?[J]. **Am J Gastroenterol**, 2006, 101(3): 524-532.

[5] SUMI A, AKIBA J, OGASAWARA S, et al. Des-γ-carboxyprothrombin (DCP) and NX-DCP expressions and their relationship with clinicopathological features in hepatocellular carcinoma[J/OL]. **PLoS One**, 2015, 10(3): e0118452.

[6] HSU H C, CHENG W, LAI P L. Cloning and expression of a developmentally regulated transcript MXR7 in hepatocellular carcinoma: biological significance and temporospatial distribution[J]. **Cancer Res**, 1997, 57(22): 5179-5184.

[7] HU B, TIAN X, SUN J, et al. Evaluation of individual and combined applications of serum biomarkers for diagnosis 7of hepatocellular carcinoma: a meta-analysis[J]. **Int J Mol Sci**, 2013, 14(12): 23559-23580.

[8] CHEN J, WU G, LI Y. Evaluation of serum des-gamma-carboxy prothrombin for the diagnosis of hepatitis B virus-related hepatocellular carcinoma: a meta-analysis[J]. **Dis Markers**, 2018, 2018: 8906023.

[9] HUSSEIN T D. Serological tumor markers of hepatocellular carcinoma: a meta-analysis[J/OL]. **Int J Biol Markers**, 2015, 30(1): e32-42.

[10] CUI R, HE J, ZHANG F, et al. Diagnostic value of protein induced by vitamin K absence (PIVKAⅡ) and hepatoma-specific band of serum gamma-glutamyl transferase (GGTⅡ) as hepatocellular carcinoma markers complementary to alpha-fetoprotein[J]. **Br J Cancer**, 2003, 88(12): 1878-1882.

[11] WANG C S, LIN C L, LEE H C, et al. Usefulness of serum des-gamma-carboxy prothrombin in detection of hepatocellular carcinoma[J]. **World J Gastroenterol**, 2005, 11(39): 6115-6119.

[12] KIM M J, BAE K W, SEO P J, et al. Optimal cut-off value of PIVKA-Ⅱ for diagnosis of hepatocellular carcinoma—using ROC curve[J]. **Korean J Hepatol**, 2006, 12(3): 404-411.

[13] VOLK M L, HERNANDEZ J C, SU G L, et al. Risk factors for hepatocellular carcinoma may impair the performance of biomarkers: a comparison of AFP, DCP, and AFP-L3[J]. **Cancer Biomark**, 2007, 3(2): 79-87.

[14] BEALE G, CHATTOPADHYAY D, GRAY J, et al. AFP, PIVKAⅡ, GP3, SCCA-1 and follisatin as surveillance biomarkers for hepatocellular cancer in non-alcoholic and alcoholic fatty liver disease[J]. **BMC Cancer**, 2008, 8: 200.

[15] YOON Y J, HAN K H, KIM D Y. Role of serum prothrombin induced by vitamin K absence or antagonist-Ⅱ in the early detection of hepatocellular carcinoma in patients with chronic hepatitis B virus infection[J]. **Scand J Gastroenterol**, 2009, 44(7): 861-866.

[16] 李 鹏，翟 云，刘 晖，等. 血清AFP、GPC3、VEGF、IGF-Ⅱ单独及联合检测对原发性肝细胞癌的诊断价值[J]. **世界华人消化杂志**, 2010, 18(25): 2702-2706.
LI Peng, ZHAI Yun, LIU Hui, et al. Diagnostic value of serum AFP alone or in combination with glypican 3, VEGF or IGF-Ⅱ for patients with primary hepatocellular carcinoma[J]. **World Chinese Journal of Digestology**, 2010, 18(25): 2702-2706. (in Chinese)

[17] LEE H J, YEON J E, SUH S J, et al. Clinical utility of plasma glypican-3 and osteopontin as biomarkers of hepatocellular carcinoma[J]. **Gut and liver**, 2014, 8(2): 177-185.

[18] OZKAN H, ERDAL H, KOÇAK E, et al. Diagnostic and prognostic role of serum glypican 3 in patients with hepatocellular carcinoma[J]. **J Clin Lab Anal**, 2011, 25(5): 350-353.

[19] ERTLE J M, HEIDER D, WICHERT M, et al. A combination of α-fetoprotein and des-γ-carboxy prothrombin is superior in detection of hepatocellular carcinoma[J]. **Digestion**, 2013, 87(2): 121-131.

[20] ABD EL GAWAD I A, MOSSALLAM G I, RADWAN N H, et al. Comparing prothrombin induced by vitamin K absence-Ⅱ (PIVKA-Ⅱ) with the oncofetal proteins glypican-3, Alpha feto protein and carcinoembryonic antigen in diagnosing hepatocellular carcinoma among Egyptian patients[J]. **J Egypt Natl Canc Inst**, 2014, 26(2): 79-85.

[21] BADR E A E, KORAH T E, GHANI A A, et al. Role of serum glypican-3 in the diagnosis and differentiation of small hepatocellular carcinoma from hepatitis-C virus cirrhosis[J]. **Alexandria J Med**, 2014, 50(3): 221-226.

[22] 马庆庆，黄建廷，童华波，等. 血清标志 Glypican-3

对肝细胞癌诊断价值初步评价[J]. **中华肿瘤防治杂志**, 2014, 21(2): 127-132.
MA Qingqing, HUANG Jianting, TONG Huabo, et al. Glypican-3, a novel tumor marker in diagnosis of human hepatocellular carcinoma[J]. **Chinese Journal of Cancer Prevention and Treatment**, 2014, 21(2): 127-132. (in Chinese)

[23] ETTE A I, NDUBUBA D A, ADEKANLE O, et al. Utility of serum des-gamma-carboxyprothrombin in the diagnosis of hepatocellular carcinoma among Nigerians, a case-control study[J]. **BMC Gastroenterol**, 2015, 15: 113.

[24] 霍 群, 郑泽辉, 刘 杰, 等. 高尔基体蛋白73及去γ-羧基凝血酶原联合甲胎蛋白检测对肝癌的诊断价值[J]. **中华医学杂志**, 2015, 95(10): 757-760.
HUO Qun, ZHENG Zehui, LIU Jie, et al. Diagnosis value of combined detection of serum golgi protein 73, desgamma carboxy prothrombin and α-fetoprotein in primary hepatic carcinoma[J]. **National Medical Journal of China**, 2015, 95(10): 757-760. (in Chinese)

[25] YU R, DING S, TAN W, et al. Performance of protein induced by vitamin K absence or antagonist-Ⅱ (PIVKA-Ⅱ) for hepatocellular carcinoma screening in Chinese population[J/OL]. **Hepat Mon**, 2015, 15(7): e28806.

[26] JEON Y, JANG E S, CHOI Y S, et al. Glypican-3 level assessed by the enzyme-linked immunosorbent assay is inferior to alpha-fetoprotein level for hepatocellular carcinoma diagnosis[J]. **Clin Mol Hepatol**, 2016, 22(3): 359-365.

[27] JI J, WANG H, LI Y, et al. Diagnostic evaluation of des-gamma-carboxy prothrombin versus α-fetoprotein for hepatitis B virus-related hepatocellular carcinoma in China: a large-scale, multicentre study[J/OL]. **PLoS One**, 2016, 11(4): e0153227.

[28] PARK S J, JANG J Y, JEONG S W, et al. Usefulness of AFP, AFP-L3, and PIVKA-Ⅱ, and their combinations in diagnosing hepatocellular carcinoma[J/OL]. **Medicine (Baltimore)**, 2017, 96(11): e5811.

[29] SUN B, HUANG Z, WANG B, et al. Significance of glypican-3 (GPC3) expression in hepatocellular cancer diagnosis[J]. **Med Sci Monit**, 2017, 23: 850-855.

[30] QIN Q F, WENG J, XU G X, et al. Combination of serum tumor markers dickkopf-1, DCP and AFP for the diagnosis of primary hepatocellular carcinoma[J]. **Asian Pac J Trop Med**, 2017, 10(4): 409-413.

[31] FARAG R M M A, ALAYOBI D, ALSALEH K A, et al. Influence of glypican-3 as a newly diagnostic biomarker in early detection of hepatocellular carcinoma among Saudi patients[J]. **BPJ**, 2018, 11(4): 1789-1796.

[32] PAN Y, DAI J, HUA X, et al. The value of combined detection of PIVKA-Ⅱ, AFP and AFP-L3 in the diagnosis of hepatocellular carcinoma[J]. **Acta Medica Mediterr**, 2019, 35(5): 2793-2797.

[33] SONG T, WANG L, SU B, et al. Diagnostic value of alpha-fetoprotein, Lens culinaris agglutinin-reactive alpha-fetoprotein, and des-gamma-carboxyprothrombin in hepatitis B virus-related hepatocellular carcinoma [J]. **J Int Med Res**, 2020, 48(3): 300060519889270.

[34] WANG Q, CHEN Q, ZHANG X, et al. Diagnostic value of gamma-glutamyltransferase/aspartate aminotransferase ratio, protein induced by vitamin K absence or antagonist Ⅱ, and alpha-fetoprotein in hepatitis B virus-related hepatocellular carcinoma[J]. **World J Gastroenterol**, 2019, 25(36): 5515-5529.

[35] CAVIGLIA G P, CIRUOLO M, ABATE M L, et al. Alpha-fetoprotein, protein induced by vitamin K absence or antagonist Ⅱ and glypican-3 for the detection and prediction of hepatocellular carcinoma in patients with cirrhosis of viral etiology[J]. **Cancers (Basel)**, 2020, 12(11): 3218.

[36] SONG T, WANG L, XIN R, et al. Evaluation of serum AFP and DCP levels in the diagnosis of early-stage HBV-related HCC under different backgrounds[J]. **J Int Med Res**, 2020, 48(10): 300060520969087.

[37] CHEN J, TANG D, XU C, et al. Evaluation of serum GDF15, AFP, and PIVKA-Ⅱ as diagnostic markers for HBV-associated hepatocellular carcinoma[J]. **Lab Med**, 2021, 52(4): 381-389.

[38] XU F, ZHANG L, HE W, et al. The diagnostic value of serum PIVKA-Ⅱ alone or in combination with AFP in Chinese hepatocellular carcinoma patients[J]. **Dis Markers**, 2021, 2021: 8868370.

[39] 郝 锐, 郑雪松, 张莲莲, 等. 5种血清标志物在肝癌诊断中的应用价值[J]. **中国地方病防治杂志**, 2018, 33(2): 125-127.
HAO Rui, ZHENG Xuesong, ZHANG Lianlian, et al. Application value of five serum markers in the diagnosis of hepatocellular carcinoma[J]. **Chinese Journal of Control of Endemic Diseases**, 2018, 33(2): 125-127. (in Chinese)

[40] 田江川. 血清异常凝血酶原、磷脂酰肌醇蛋白聚糖-3、甲胎蛋白联合检测对HBV相关HCC的诊断价值分析[J]. **实用医院临床杂志**, 2019, 16(2): 143-146.
TIAN Jiangchuan. The diagnostic value of combined detection of serum DCP, GPC3 and AFP for HBV-associated HCC[J]. **Practical Journal of Clinical Medicine**, 2019, 16(2): 143-146. (in Chinese)

[41] 王 妮. 磷脂酰肌醇蛋白聚糖-3在肝癌中的表达及其临床应用价值[D]. 昆明: 昆明医科大学, 2020.
WANG Ni. Expression and clinical application of phosphatidylinositol proteoglycan-3 in liver cancer[D]. Kunming: Kunming Medical University, 2020. (in Chinese)

[42] VOGEL A, MEYER T, SAPISOCHIN G, et al. Hepatocellular carcinoma[J]. **Lancet**, 2022, 400(10360): 1345-1362.

[43] LI C, LI R, ZHANG W. Progress in non-invasive detection of liver fibrosis[J]. **Cancer Bio Med**, 2018,

15(2): 124-136.

[44] TAKETA K. Alpha-fetoprotein: reevaluation in hepatology [J]. **Hepatology**, 1990, 12(6): 1420-1432.

[45] 中华人民共和国国家卫生健康委员会医政医管局. 原发性肝癌诊疗规范(2019年版)[J]. **肿瘤综合治疗电子杂志**, 2020, 6(2): 55-85.
Department of Medical Affairs Administration, Ministry of Health of the PRC. Diagnostic and therapeutic criteria for primary liver cancer(2019)[J]. **Journal of Multidisciplinary Cancer Management (Electronic Version)**, 2020, 6(2): 55-85. (in Chinese)

[46] MIZEJEWSKI G J. Alpha-fetoprotein structure and function: relevance to isoforms, epitopes, and conformational variants[J]. **Exp Biol Med (Maywood)**, 2001, 226(5): 377-408.

[47] CALDERARO J, COUCHY G, IMBEAUD S, et al. Histological subtypes of hepatocellular carcinoma are related to gene mutations and molecular tumour classification[J]. **J Hepatol**, 2017, 67(4): 727-738.

[48] LAZAREVICH N L. Molecular mechanisms of alpha-fetoprotein gene expression[J]. **Biochemistry (Mosc)**, 2000, 65(1): 117-133.

[49] LI M S, LI P F, HE S P, et al. The promoting molecular mechanism of alpha-fetoprotein on the growth of human hepatoma Bel7402 cell line[J]. **World J Gastroenterol**, 2002, 8(3): 469-475.

[50] LIN B, ZHU M, WANG W, et al. Structural basis for alpha fetoprotein-mediated inhibition of caspase-3 activity in hepatocellular carcinoma cells[J]. **Int J Cancer**, 2017, 141(7): 1413-1421.

[51] DUDICH E, SEMENKOVA L, DUDICH I, et al. Alpha-fetoprotein antagonizes X-linked inhibitor of apoptosis protein anticaspase activity and disrupts XIAP-caspase interaction[J]. **FEBS J**, 2006, 273(16): 3837-3849.

[52] BAIG J A, ALAM J M, MAHMOOD S R, et al. Hepato-cellular carcinoma (HCC) and diagnostic significance of a-fetoprotein (AFP)[J]. **J Ayub Med Coll Abbottabad**, 2009, 21(1): 72-75.

[53] YANG Y, LI G, LU Z, et al. Progression of prothrombin induced by vitamin K absence-Ⅱ in hepatocellular carcinoma[J]. **Front Oncol**, 2021, 11: 726213.

[54] DONG L, QIU X, GAO F, et al. Protein induced by vitamin K absence or antagonist Ⅱ: experience to date and future directions[J]. **Biochim Biophys Acta Rev Cancer**, 2023, 1878(6): 189016.

[55] DOU W T, QIU P, SHI Y, et al. Orthogonally engineered albumin with attenuated macrophage phagocytosis for the targeted visualization and phototherapy of liver cancer[J]. **J Am Chem Soc**, 2023, 145(31): 17377-17388.

[56] FANG Y S, WU Q, ZHAO H C, et al. Do combined assays of serum AFP, AFP-L3, DCP, GP73, and DKK-1 efficiently improve the clinical values of biomarkers in decision-making for hepatocellular carcinoma? A meta-analysis[J]. **Expert Rev Gastroenterol Hepatol**, 2021, 15(9): 1065-1076.

[57] CAVIGLIA G P, RIBALDONE D G, ABATE M L, et al. Performance of protein induced by vitamin K absence or antagonist-Ⅱ assessed by chemiluminescence enzyme immunoassay for hepatocellular carcinoma detection: a meta-analysis[J]. **Scand J Gastroenterol**, 2018, 53(6): 734-740.

[58] XU D, SU C, SUN L, et al. Performance of serum glypican 3 in diagnosis of hepatocellular carcinoma: a meta-analysis[J]. **Ann Hepatol**, 2019, 18(1): 58-67.

[59] XU C, YAN Z, ZHOU L, et al. A comparison of glypican-3 with alpha-fetoprotein as a serum marker for hepatocellular carcinoma: a meta-analysis[J]. **J Cancer Res Clin Oncol**, 2013, 139(8): 1417-1424.

[60] LIU J W, ZUO X L, WANG S. Diagnosis accuracy of serum glypican-3 level in patients with hepatocellular carcinoma and liver cirrhosis: a meta-analysis[J]. **Eur Rev Med Pharmacol Sci**, 2015, 19(19): 3655-3673.

［本文编辑　余　方　刘丽娜］

·读者·作者·编者·

作者投稿时请提供ORCID

开放研究者与贡献者身份识别码(open researcher and contributor identifier，ORCID)是由汤森路透和自然出版集团等单位于2009年共同发起创建的，其意义与科学文献领域的数字对象标识符(DOI)类似：DOI为科技文献的身份证，一文一证；ORCID为科研人员的学术身份证，一人一证。若尚未获取ORCID的作者请先登录https://orcid.org，注册后免费获取ORCID。本刊从2015年第3期起在作者信息栏添加ORCID，即https://orcid.org后16位数字。如贺晶ORCID为0000-0002-9579-9593，作者信息最后加上https://orcid.org/0000-0002-9579-9593。