# 肝癌筛查研究进展

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**摘　要**：肝癌是我国常见的恶性肿瘤之一，严重威胁居民健康，全球近一半的新发和死亡病例发生在中国。危险因素的复杂多样为推行肝癌一级预防带来了一定困难。在高危人群中进行筛查和早诊早治是降低肝癌负担的有效措施。确定肝癌高危人群和选择合适的筛查方法是肝癌筛查的重点和难点。肝癌发病风险预测模型是识别和浓缩肝癌高危人群的有力工具。融合基因、临床指标、分子标志物和肝癌独立危险因素已成为构建和优化肝癌发病风险预测模型的新趋势。目前研究已证实筛查可以显著提高筛查人群生存率，但能否降低肝癌死亡率尚无定论。精准定位高危人群，优化筛查流程，提高早期检出率是下一步研究的重点。同时还应加强人群健康教育，普及防治知识以提高居民对癌症筛查的认识和参与度。

**关键词**：肝癌；筛查
**中图分类号**：R735.7　　**文献标识码**：A　　**文章编号**：1004-0242(2020)12-0925-08
doi：10.11735/j.issn.1004-0242.2020.12.A007

## Research Progress of Liver Cancer Screening

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**Abstract**：Liver cancer is one of the most common cancers，nearly half cases and deaths globally occur in China，posing a great threat to human health and lives. The complexity and diversity of risk factors make it difficult to implement primary prevention of liver cancer. The early detection and treatment through screening high-risk population is an effective measure to reduce liver cancer burden. To identify high-risk population and to use appropriate screening methods are the key issues for liver cancer screening. Risk prediction model for liver cancer is a useful tool to identify high-risk population of liver cancer，which can be optimized by the combination of gene detection，clinical indicator，biomarker and risk factor assessment. Accurate identifying high-risk individuals，optimizing screening procedures，and improving early detection rate should be focused for further researches. The healthy education and knowledge popularization on cancer prevention and control are necessary for improving the awareness and increasing participation rates for liver cancer screening among residents.

**Key words**：liver cancer；screening

肝癌是全球常见的恶性肿瘤之一。Globocan2018 显示，全球肝癌新发病例数为 84.1 万例，死亡病例数为 78.1 万例，居恶性肿瘤发病第 6 位、死亡第 4 位。中国肝癌发病和死亡人数分别占全球的 46.6% 和 47.1%[1]。我国最新肿瘤登记数据显示，2015 年全国肝癌新发病例数约 37.0 万例，因肝癌死亡人数约 32.6 万例[2]，严重危害居民健康。

肝癌危险因素复杂多样，常见的危险因素包括乙肝病毒感染（hepatitis B virus，HBV）、丙肝病毒感染（hepatitis C virus，HCV）、黄曲霉毒素以及各种原因导致的肝硬化等[3-5]。由于我国人口基数较大且肝癌病因繁杂，针对病因的一级预防存在不完善、收效滞后等问题。肝癌预后与肝癌诊断时肝功能状态密切相关。早期肝癌通过手术治疗生存率可接近 70%，而晚期肝癌平均生存时间小于 1 年[6]。我国肝癌 5 年相对生存率仅 12.1%[7]，多数肝癌患者就诊时已处于晚期阶段。日本于 2002 年开始对 40 岁以上的 HBV 和 HCV 感染者进行肝癌筛查[8]，肝癌 5年相对生存率显著大于中国[9]。因此，肝癌早诊早治对

收稿日期：2020-05-23；修回日期：2020-07-05
**基金项目**：中国医学科学院医学与健康科技创新工程(2019-I2M-2-004)；深圳医疗卫生三名工程(SZSM201911015)
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于降低我国肝癌疾病负担尤为重要。

## 1 肝癌筛查的目标人群

### 1.1 肝癌高危人群

肝癌发生基于一定的疾病风险，在一般人群中实行肝癌筛查可能不具有成本效益。因而，如何有效、准确地选择筛查对象是提高筛查效率的关键点。2019 年中华人民共和国国家卫生健康委员会医政医管局发布的《原发性肝癌诊疗规范(2019 年版)》的筛查和诊断部分指出，肝癌高危人群主要包括具有 HBV 和(或)HCV 感染、过度饮酒、非酒精性脂肪性肝炎、长期食用被黄曲霉毒素污染的食物、各种其他原因引起的肝硬化以及有肝癌家族史等人群，尤其是年龄>40 岁的男性风险更大[10]。然而，不同地区对肝癌高危人群定义不完全相同。韩国肝脏研究协会认为 HBV/HCV 感染者或各种原因导致的肝硬化患者为肝癌高危人群。美国肝病研究协会对人群年龄加以限定，认为亚洲男性 40 岁、女性 50 岁以上以及非洲或美国 20 岁以上 HBV/HCV 感染者和肝硬化患者为肝癌高危人群[11]。非酒精性脂肪性肝病是如今肝癌、肝硬化发生的较为常见的危险因素，但当其未发展至肝硬化时，肝癌发生风险较小[12]。2018 年美国肝脏研究协会认为 HCV 感染/非酒精性脂肪性肝病但未发展至肝硬化患者，不属于肝癌筛查的目标人群[13]。

### 1.2 肝癌高危风险评估模型

是否进行肝癌筛查取决于人群肝癌发生风险。具备不同危险因素时，肝癌发生风险不同。例如，曾经吸烟者发生肝癌风险是不吸烟者的 1.12 倍，而 HBV 感染者发生肝癌风险是非感染者的 15~20 倍[3,14]。在肝癌高危人群中实行肝癌筛查可以最大化发现潜在肝癌患者，而改善肝癌筛查效果。但如何有效在人群中发现肝癌高危个体仍存在不确定性。

通过结合人群流行病学特征和相关生物学标志物，构建肝癌发病风险预测模型是识别和浓缩肝癌高危人群的有力工具。GAG-HCC 是较早的用于预测肝癌发病风险的预测模型，该评分体系包括年龄、性别、HBV DNA、核心启动子突变以及肝硬化状态[15]。并将评分大于等于 101 作为高危人群的临界值。但并未确定可用于筛查项目的高危人群判定的最佳临界值。Wong 等[16]在 1005 例乙肝表面抗原阳性人群中构建了包含年龄、白蛋白、胆红素、HBV DNA 和肝硬化状态 5 个因素在内的总分为 0~44.5 分的 CU-HCC 评分系统。目标人群均经过长期随访、且模型经过验证，可靠性较高。但大部分人群的肝硬化是依据腹部超声予以诊断，因而可能发生漏诊，如发生分类错误则会降低肝癌风险预测的准确度。基于 CU-HCC 评分系统，Wong 等[17]构建了包含肝脏硬度(liver stiffness measurements，LSM)、年龄、白蛋白和 HBV DNA 水平 4 个指标的 LSM-HCC 预测模型，为肝癌发病风险预测提供了有用工具，且提高了 CU-HCC 的预测能力。NOMO 得分系统较为复杂，其来自于 REVEAL-HBV 队列[18]。该模型包括年龄、性别、肝癌家族史、饮酒、血清丙氨酸转氨酶浓度(amino-transferase，ALT)、HBeAg 状态、HBV DNA 水平和 HBV 的基因型，模型实用性较差。Yang 等[19]在 3584 例非肝硬化慢性 HBV 感染者中进行优化，并在韩国和香港的 1505 例慢性 HBV 感染者中进行外部验证。最终构建包含年龄、性别、ALT、HBeAg 状态以及 HBV DNA 水平，总评分 0~17 分的 REACH-B 模型。PAGE-B 是首个基于白种人建立的肝癌风险预测模型，包括年龄、性别和血小板计数。该模型简单易行，后在亚洲人群中进行优化。改良的 PAGE-B (mPAG-B)[20] 在原始模型基础上增加了白蛋白水平，以 8 分、13 分将人群分为低风险、中风险和高风险，模型预测效能更好，且更适合亚洲慢性乙肝患者的管理(Table 1)。

目前肝癌风险评分体系较多，且多基于亚洲人群构建，模型推广性较差，仍需加强模型的外部验证。建立不同种族、不同地域的人群肝癌风险预测模型对于明确肝癌高危人群至关重要。此外，基因组学和蛋白组学的发展为肝癌风险精准预测提供了新思路。研究表明基因表达与肝癌发生风险密切相关[21]。2019 年中国学者基于 13 个与肝癌预后显著相关的信号通路构建肝癌风险预测模型，表现了基于信号通路水平特征的模型在预测肝癌风险的优势[22]。融合基因、临床指标、分子标志物和肝癌独立危险因素成为未来构建和优化肝癌发病风险预测模型的新趋势。

## 2 肝癌筛查方法

### 2.1 影像学技术

最佳的筛查技术需要具备高灵敏度、低成本和

可及性等特征。超声因价格低廉,没有侵略性和辐射而成为多个肝病研究组织推荐的影像学技术[11]。Meta 结果分析显示超声筛查的灵敏度和特异性分别为 51%~87%和 80%~100%[31],发现早期肝癌(Milan Criteria 标准)的灵敏度是 33%~61%[32]。但腹部超声容易受患者特征(肥胖、患病位置)、临床医生的操作能力和临床经验所影响。适当地结合生物标志物如血清甲胎蛋白 (alpha-feta protein, AFP)可能会增加筛查的准确度[33]。为评价不同肝癌筛查技术的准确性,严永锋等[34]通过系统综述方法对 54 篇研究进行整合,共包含 47 728 例患者,结果显示 AFP 联合腹部超声检查可大幅提高诊断灵敏度, 适合于高危人群筛查。当腹部超声筛查的灵敏度为 92.0%时,联合 AFP 进行筛查时其灵敏度增加至 99.2%[35]。

CT 和 MRI 通常能发现更多肝癌患者, 灵敏度分别为 63%~76%和 77%~90%[31]。但因高成本、高假阳性率以及辐射暴露等原因而不适合大规模、长期人群筛查。研究表明一次腹部 CT 平扫(240mAs)含有至少 20mGy 的辐射量[36]。MRI 虽然能准确显示其他检查手段(如 CT 等)无法显示的病变。但价格更昂贵且费时[37]。对<1cm 的肝癌病灶和肝硬化并发肝癌的显示效果不理想[38](Table 2)。相比于腹部超声,CT 与 MRI 则更注重临床诊断价值,腹部超声仍是目前最常使用和推荐的影像学方法。

### 2.2 血清学标志物

AFP 是目前应用较为广泛的血清学生物标志物。它是胚胎内胚层合成的一种糖蛋白[39],在正常成人血循环中含量极微(<20μg/L)。但怀孕和某些良性病变包括急慢性肝炎、肝硬化患者以及某些生殖胚胎性肿瘤 (如睾丸癌)均可使得 AFP 含量升高,从而造成假阳性。AFP 灵敏度较差,约为 40%~65%。当病变<3cm,其灵敏度更低,约为 25%[40]。通过提高 AFP 正常值的上限(20μg/L),可以更好指导现场应用。目前,多以 AFP 血清含量>400μg/L 作为肝癌诊断阈值。

甲胎蛋白异质体(AFP-L3)是肝癌细胞所特有的一种物质,对于肝癌的早发现、早诊断有着重要的意义。一项前瞻性多中心研究表明 AFP-L3 具有较高的特异性(92%),但灵敏度较低(37%)而不适合用于人群筛查[41]。GP73(golgi protein 73,GP73)是高尔基体 2 型跨膜蛋白,当肝细胞受到病毒感染时可引起 GP73 高表达,而在健康人体内含量极微[42],与肝硬化患者相比,其鉴别肝癌的灵敏度和特异性分别为 69%和 75%[43], 且其含量与肿瘤大小、病理分期无关,是一种具有应用前景的肿瘤标志物[44]。

**Table 1 The risk prediction model for liver cancer**

| Year | Models | Etiology | Regions | Race | N | Variables |
|---|---|---|---|---|---|---|
| 2009 | GAG-HCC[15] | HBV | Hong Kong | Asian | 820 training, internal validation | Age, sex, HBV DNA, core promoter mutations, cirrhosis |
| 2010 | CU-HCC[16] | HBV | Hong Kong | Asian | 1005 training,424 validation | Age, albumin, bilirubin, HBV DNA, cirrhosis |
| 2010 | NOMO[18] | HBV | Taiwan | Asian | 2435 training,1218 validation | Age, sex, HCC family history, alcohol, ALT, HBeAg, HBV DNA, HBV genotype |
| 2011 | REACH-B[19] | HBV | Taiwan | Asian | 3584 training,1505 validation | Age, sex, ALT, HBeAg, HBV DNA |
| 2014 | LSM-HCC[17] | HBV | Hong Kong | Asian | 1035 training,520 validation | LSM, age, albumin, HBV DNA |
| 2015 | Hung et al[23] | HBV | Taiwan | Asian | 8252 training,4125 validation | Age, sex, ALT, previous chronic liver disease, family history of HCC, smoking |
| 2015 | FIB-4[24] | HBV | Korea | Asian | 986 training,without validation | AST, ALT, age |
| 2016 | PAGE-B[25] | HBV | Caucasia | European | 1325 training,490 validation | Age, sex, platelet |
| 2017 | Sohn et al[26] | HBV | Korea | Asian | 990 training,1071 validation | Age, sex, cirrhosis |
| 2017 | THRI[27] | HBV and others* | Toronto | North American | 2079 training,1144 validation | Age, sex, etiology, platelet |
| 2018 | mPAGE-B[28] | HBV | Korea | Asian | 1896 training,948 validation | Age, sex, platelet, albumin |
| 2018 | CAMD[29] | HBV | Taiwan | Asian | 23851 training,19321 validation | Cirrhosis, age, sex, diabetes |
| 2019 | AGED[30] | HBV | Qidong | Asian | 1388 training,1663 validation | Age, sex, HBeAg, HBV DNA |

Note:*:HCV-No SVR,HCV-SVR,Steatohepatitis,Autoimmune and other

**Table 2　Imaging modalities for the screening of liver cancer**

| Index | Ultrasound | CT | MRI |
|---|---|---|---|
| Sensitivity | 51%~87% | 63%~76% | 77%~90% |
| Specificity | 80%~100% | 87%~98% | 84%~97% |
| Advantages | Easy-to-operation, real-time, no ionizing radiation, less expensive | High specificity | No ionizing radiation, high specificity |
| Disadvantages | Limited in obese patients and highly dependent on the expertise of its operator | Ionizing radiation exposure, high cost | Less sensitive for small lesions (<1cm) and liver cancer combined with cirrhosis, more time-consuming, high cost |

维生素K缺乏或拮抗剂-Ⅱ诱导产生的蛋白(protein induced by vitamin K absence or antagonist-Ⅱ,PIVKA-Ⅱ)又称异常凝血酶原,它是肝脏合成的无凝血活性的异常凝血酶原。在AFP<20μg/L的人群中,其鉴别肝癌的灵敏度和特异性分别为57.9%和95.9%。当和AFP-L3联合使用时,灵敏度和特异性分别为92.1%和79.7%[45]。PIVKA-Ⅱ具有良好的预测能力,可用于肝癌的常规筛查[46]。目前,亚太肝病学会[47]、日本肝病学[48]、《2019年原发性肝癌诊疗规范》中的筛查与诊断部分[10]均已将PIVKA-Ⅱ写入指南中,可以作为肝癌筛查和辅助诊断的重要指标。

### 2.3　表观遗传学标志物

MicroRNA(miRNAs)及DNA的甲基化在肿瘤的发生发展起着重要作用。研究表明miRNA在肝癌组织与正常组织的表达谱存在显著差异,因而可能成为肝癌诊断的新型特异性生物学标志物[49]。Zhou等[50]发现microRNA组(miR-122、miR-192、miR-21、miR-223、miR-26a、miR-27a和miR-801)可以较好的区分肝癌与正常人(AUC=0.941)以及肝硬化患者(AUC=0.884)。中国学者从血浆中筛选的7个血清miRNA组成的分类器检测肝癌的灵敏度(70.4%~85.7%)远高于血清AFP(40.7%~69.4%),尤其是检测小肝癌(肿瘤大小≤3cm)和早期肝癌(BCLC 0期及A期)的优势更加明显[51]。越来越多研究证实,异常DNA甲基化是肿瘤发生的早期事件。Hao等[52]发现DNA甲基化可以有效区分正常组织和肿瘤组织,并有潜力成为恶性肿瘤诊断和监测的新型标志物。Xu等[53]在715例肝癌患者和560名健康对照的血浆样本中,从401个甲基化位点中筛选出了肝癌患者外周血中ctDNA的10个特异性甲基化位点可有效地将肝癌患者与正常人群加以区分,灵敏度和特异性分别为85.7%和94.3%,效果优于传统AFP检测。这些新型肿瘤学标志物的不断发现,为未来有效识别肝癌奠定了重要基础。

## 3　肝癌筛查间隔

合适的筛查间隔可以最大化肝癌筛查效益,既能较多地发现早期病例,亦可以减少经济损耗。在法国和比利时两个国家43个中心开展的一项随机对照试验中共纳入1278例肝硬化患者,通过对比3个月组和6个月组肝癌筛查效果,发现3个月组只比6个月组多检出局灶性病变,肝癌发病率没有显著性差异[54]。在中国台湾开展一项随机对照研究中,通过对比4个月组与12个月组肝癌生存率,结果表明两组生存率亦没有统计学差异[55]。而6个月组与12个月组相比,不仅能发现极早期的肝癌病例,且可减少晚期癌的比例[56]。平均而言,在肝硬化患者中每半年进行腹部超声检查,可以增加8.6个月的质量调整寿命年[57]。目前,多个肝癌管理指南均推荐肝癌高危人群每隔6个月进行一次肝癌筛查[11]。2009年我国出版的《中国癌症筛查及早诊早治技术方案》中,也认为半年一次是较为合适的筛查间隔[58]。

## 4　肝癌筛查效果评价

### 4.1　死亡率

目前,除国内外肝病研究协会发布的肝癌管理指南外,国际或国内尚无标准化的指南推荐肝癌筛查,且对于肝癌筛查效果仍存在争议[59]。死亡率是评估筛查是否有效的唯一且最直接的指标。至今,全球只有两项评估肝癌筛查能否降低死亡率的随机对照试验,且均开展于中国。Zhang等[60]在上海开展的一项随机对照试验共纳入35~59岁且HBV感染呈阳性或具有慢性肝炎史的人群18 816例。其中9373例随机分类为筛查组,9443例为对照组。每间隔6个月对筛查组人群的甲胎蛋白含量进行测定和腹部超声检查。结果显示通过筛查可以使肝癌的死亡率

降低 37%。Chen 等[61]于 1989 年在中国启东首次开展高危人群随机对照试验。结果表明两组人群死亡率相似且不存在统计学差异。两项随机对照试验均在方法学方面存在较大失误而降低其参考价值[62]。

中国台湾学者开展的观察性研究认为肝癌筛查可能有效降低肝癌死亡率。Yeh 等[63]对不同危险级别的人群有针对地行 AFP 检测和腹部超声筛查，结果表明在台湾彰化县，通过筛查可以使肝癌死亡率降低 31%。Chen 等[64]利用 2 阶段方法(即先确定高危人群，后在高危人群进行腹部超声检查）在 4843 人中进行肝癌筛查，平均随访 7 年后，结果表明肝癌筛查可使肝癌死亡率降低 41%(Table 3)。Ji 等[65]通过对 17 966 例参与肝癌筛查的社区人群随访 4 年后仍未发现肝癌筛查可有效降低肝癌死亡率。筛查手段、项目实施质量、人群参与率、随访时间以及治疗效果等均能影响肝癌筛查效果。肝癌筛查是否有效降低肝癌死亡率仍需国内外大型前瞻性研究予以支持。

### 4.2 生存率

目前尚没有高质量 RCT 表明肝癌筛查能降低肝癌死亡率，但已明确肝癌筛查可以明显改善人群生存率。Singal 等[66]对 47 篇肝癌筛查效果的队列研究和病例对照研究进行系统综述，纳入人群共 15 158 人，其中 6284 例(41.4%)被诊断为肝癌，表明肝癌监测可以明显改善筛查人群生存率（OR=1.90，95%CI：1.67~2.17)。Mcmahon 等[67]对 1487 例慢性 HBV 携带者进行长期随访，历时 16 年发现肝癌筛查可以有效发现早期病变。此外，澳大利亚[68]和日本学者[69]分别于 2005 年和 2006 年证实肝癌筛查可以明显改善人群肝癌生存率。陈建国等人通过对比每年参加 2 次的筛查和不能连续参加定期筛查的 268 例肝癌患者的生存率，结果表明前者 1、3、5、8 年生存率分别为 77.16%、49.04%、38.53%和 24.25%，后者 1、3、5、8 年生存率分别为 36.25%、21.21%、21.21%和 0%，差异均有统计学意义（$P$ 均<0.05）[59]。这表明定期筛查更有可能发现早期肝癌，从而改善生存率。

总之，通过构建肝癌高危风险评估模型是浓缩肝癌在肝癌高危人群的有效方式。虽然高特异性和灵敏度的新型肿瘤学标志物不断发现，AFP 对肝癌筛查和辅助诊断仍有价值。目前认为每半年进行腹部超声联合 AFP 检查可能是肝癌筛查的最佳方法。有充分证据提示肝癌筛查可以显著改善筛查人群生存率，但能否降低人群肝癌死亡率仍需大型前瞻性队列研究予以

**Table 3 Evaluation of the effectiveness of screening for liver cancer**

| Index | Author/Year | Country | Recruitment time | Study design | N | Modality | Conclusion |
|---|---|---|---|---|---|---|---|
| Mortality | J-G Chen/2003[61] | China | 1989—1995 | RCT | 5581 (3712 *vs* 1869) | AFP+ALT | The mortality rate was not significant in the screening and control group(RR=0.83, 95%CI:0.68~1.03) |
| | Bo-Heng Zhang/2004[70] | China | 1993—1995 | RCT | 18816 (9373 *vs* 9443) | US+AFP | Screening reduced HCC mortality by 37% (RR=0.63, 95%CI:0.41~0.98) |
| | Yen-Po Yeh/2014[63] | China | 2008—2010 | Community-based trial | 41219 (11114 *vs* 30105) | US | Screening reduced HCC mortality by 31% (RR=0.69, 95%CI:0.56~0.84) |
| | Hashem B El-Serag/2011[71] | USA | 1998—2007 | A retrospective cohort study | 1480 (1148 *vs* 332) | US+AFP | Screening is rather modest in reducing HCC-related mortality (HR=0.97,95%CI:0.83~1.15) |
| | Mingfang Ji/2018[65] | China | 2012 | Community-based trial | 68510 (17966 *vs* 50544 ) | US+AFP | Screening does not show a reduction in liver cancer mortality (RR=1.04, 95%CI:0.68~1.58) |
| Survival | Brian J. Mcmahon/2000[67] | Alaska | 1982—1987 | A population-based prospective cohort | 1487 *vs* historical controls | US+AFP | Screening prolonged survival rates significantly ($P$<0.001) |
| | Kemp/2005[68] | Australia | 1994—2002 | Hospital-based prospective cohort | No Report | US/AFP | Screening improves patient survival (3 year: 38% *vs* 19%, $P$<0.001) |
| | Hironori Tanaka/2006[69] | Japan | 1991—2003 | A retrospective cohort study | 384 (182 *vs* 202) | US+AFP | Screening improves patient survival (5 year: 46% *vs* 32%, $P$<0.001) |

支持。此外，我国肝癌筛查目前仍面临人群参与率不足、高危人群定位不明确等问题。如何有效、最大化推动肝癌筛查，仍需要各级政府和大众的理解与支持，我国肝癌筛查任重而道远。

## 参考文献


[1] Global Cancer Observatory：Cancer Today. Lyon，France：International Agency for Research on Cancer [EB/OL]. https://gco.iarc.fr/today. Accessed 20 March 2020.

[2] An L，Zeng HM，Zheng RS，et al. Liver cancer epidemiology in China，2015[J]. Chinese Journal of Oncology，2019，41(10)：721-727. [安澜，曾红梅，郑荣寿，等. 2015 年中国肝癌流行情况分析 [J]. 中华肿瘤杂志，2019，41(10)：721-727.]

[3] Massarweh NN，El-Serag HB. Epidemiology of hepatocellular carcinoma and intrahepatic cholangiocarcinoma [J]. Cancer Control，2017，24(3)：1073274817729245.

[4] Wallace MC，Preen D，Jeffrey GP，et al. The evolving epidemiology of hepatocellular carcinoma：a global perspective [J]. Expert Rev Gastroenterol Hepatol，2015，9(6)：765-779.

[5] Mak LY，Cruz-Ramon V，Chinchilla-Lopez P，et al. Global epidemiology，prevention，and management of hepatocellular carcinoma[J]. Am Soc Clin Oncol Educ Book，2018，38：262-279.

[6] Singal AG，Yopp A，Skinner C，et al. Utilization of hepatocellular carcinoma surveillance among American patients：a systematic review [J]. J Gen Intern Med，2012，27(7)：861-867.

[7] Zeng H，Chen W，Zheng R，et al. Changing cancer survival in China during 2003-15：a pooled analysis of 17 population-based cancer registries[J]. Lancet Glob Health，2018，6(5)：e555-e567.

[8] Song P，Gao J，Inagaki Y，et al. Biomarkers：evaluation of screening for and early diagnosis of hepatocellular carcinoma in Japan and China[J]. Liver Cancer，2013，2(1)：31-39.

[9] Allemani C，Matsuda T，Di Carlo V，et al. Global surveillance of trends in cancer survival 2000-14 (CONCORD-3)：analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries [J]. Lancet (London，England)，2018，391(10125)：1023-1075.

[10] Diagnosis and Treatment of Primary Liver Cancer (2019 Edition) [EB/OL]. http://wsjkw.shandong.gov.cn/wzxxgk/tzwj/202001/t20200119_2509499.html. Accessed 5 July 2020.[原发性肝癌诊疗规范(2019 年版)[EB/OL]. http://wsjkw.shandong.gov.cn/wzxxgk/tzwj/202001/t20200119_ 2509499.html. Accessed 5 July 2020.]

[11] Ronot M，Pommier R，Dioguardi Burgio M，et al. Hepatocellular carcinoma surveillance with ultrasound-cost-effectiveness，high-risk populations，uptake [J]. Br J Radiol，2018，91(1090)：20170436.

[12] Kanwal F，Singal AG. Surveillance for hepatocellular carcinoma：current best practice and future direction[J]. Gastroenterology，2019，157(1)：54-64.

[13] Marrero JA，Kulik LM，Sirlin CB，et al. Diagnosis，staging，and management of hepatocellular carcinoma：2018 Practice Guidance by the American Association for the Study of Liver Diseases[J]. Hepatology，2018，68(2)：723-750.

[14] Bosetti C，Turati F，La Vecchia C. Hepatocellular carcinoma epidemiology [J]. Best Pract Res Clin Gastroenterol，2014，28(5)：753-770.

[15] Yuen MF，Tanaka Y，Fong DY，et al. Independent risk factors and predictive score for the development of hepatocellular carcinoma in chronic hepatitis B [J]. J Hepatol，2009，50(1)：80-88.

[16] Wong VWS，Chan SL，Mo F，et al. Clinical scoring system to predict hepatocellular carcinoma in chronic hepatitis B carriers[J]. J Clin Oncol，2010，28(10)：1660-1665.

[17] Wong GL，Chan HL，Wong CK，et al. Liver stiffness-based optimization of hepatocellular carcinoma risk score in patients with chronic hepatitis B [J]. J Hepatol，2014，60(2)：339-345.

[18] Yang HI，Sherman M，Su J，et al. Nomograms for risk of hepatocellular carcinoma in patients with chronic hepatitis B virus infection[J]. J Clin Oncol，2010，28(14)：2437-2444.

[19] Yang HI，Yuen MF，Chan HL，et al. Risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B)：development and validation of a predictive score [J]. Lancet Oncol，2011，12(6)：568-574.

[20] Lee HW，Kim SU，Park JY，et al. External validation of the modified PAGE-B score in Asian chronic hepatitis B patients receiving antiviral therapy [J]. Liver Int，2019，39(9)：1624-1630.

[21] Hoshida Y，Villanueva A，Kobayashi M，et al. Gene expression in fixed tissues and outcome in hepatocellular carcinoma[J]. N Engl J Med，2008，359(19)：1995-2004.

[22] Fa B，Luo C，Tang Z，et al. Pathway-based biomarker identification with crosstalk analysis for robust prognosis prediction in hepatocellular carcinoma[J]. EBioMedicine，2019，44：250-260.

[23] Hung YC，Lin CL，Liu CJ，et al. Development of risk scoring system for stratifying population for hepatocellular carcinoma screening[J]. Hepatology，2015，61(6)：1934-1944.

[24] Suh B,Park S,Shin DW,et al. High liver fibrosis index FIB-4 is highly predictive of hepatocellular carcinoma in chronic hepatitis B carriers [J]. Hepatology,2015,61(4):1261–1268.

[25] Papatheodoridis G,Dalekos G,Sypsa V,et al. PAGE-B predicts the risk of developing hepatocellular carcinoma in Caucasians with chronic hepatitis B on 5-year antiviral therapy[J]. J Hepatol,2016,64(4):800–806.

[26] Sohn W,Cho JY,Kim JH,et al. Risk score model for the development of hepatocellular carcinoma in treatment-naive patients receiving oral antiviral treatment for chronic hepatitis B[J]. Clin Mol Hepatol,2017,23(2):170–178.

[27] Sharma SA,Kowgier M,Hansen BE,et al. Toronto HCC risk index:a validated scoring system to predict 10–year risk of HCC in patients with cirrhosis[J]. J Hepatol,2017,S0168–8278(17)32248–1.

[28] Kim JH,Kim YD,Lee M,et al. Modified PAGE-B score predicts the risk of hepatocellular carcinoma in Asians with chronic hepatitis B on antiviral therapy[J]. J Hepatol,2018,69(5):1066–1073.

[29] Hsu YC,Yip TC,Ho HJ,et al. Development of a scoring system to predict hepatocellular carcinoma in Asians on antivirals for chronic hepatitis B [J]. J Hepatol,2018,69(2):278–285.

[30] Fan C,Li M,Gan Y,et al. A simple AGED score for risk classification of primary liver cancer:development and validation with long-term prospective HBsAg-positive cohorts in Qidong,China[J]. Gut,2019,68(5):948.

[31] Jiang HY,Chen J,Xia CC,et al. Noninvasive imaging of hepatocellular carcinoma:from diagnosis to prognosis[J]. World J Gastroenterol,2018,24(22):2348–2362.

[32] Tzartzeva K,Obi J,Rich NE,et al. Surveillance imaging and alpha fetoprotein for early detection of hepatocellular carcinoma in patients with cirrhosis:a Meta-analysis[J]. Gastroenterology,2018,154(6):1706–1718.e1.

[33] Frenette CT,Isaacson AJ,Bargellini I,et al. A practical guideline for hepatocellular carcinoma screening in patients at risk [J]. Mayo Clin Proc Innov Qual Outcomes,2019,3(3):302–310.

[34] Yan YF,Wang YT,Zhu C,et al. The accuracy of screening technologies for liver cancer:a meta-analysis [J]. Chinese Journal of Evidence-Based Medicine,2018,18 (15):418–427. [严永锋,王宇婷,朱陈,等. 肝癌筛查技术准确性的Meta 分析[J]. 中国循证医学杂志,2018,18(15):418–427.]

[35] Chang TS,Wu YC,Tung SY,et al. Alpha-fetoprotein measurement benefits hepatocellular carcinoma surveillance in patients with cirrhosis [J]. Am J Gastroenterol,2015,110(6):836–44;quiz 845.

[36] Brenner DJ,Hall EJ. Computed tomography—an increasing source of radiation exposure [J]. N Engl J Med,2007,357(22):2277–2284.

[37] Ayoub WS,Steggerda J,Yang JD,et al. Current status of hepatocellular carcinoma detection:screening strategies and novel biomarkers[J]. Ther Adv Med Oncol,2019,11:1758835919869120.

[38] Lu LG. Advances in early screening and diagnosis of hepatocellular carcinoma [J]. Journal of Clinical Hepatology,2017,33 (7):1257–1261.[陆伦根. 原发性肝癌的早期筛查及诊断[J]. 临床肝胆病杂志,2017,33(7):1257–1261.]

[39] Wang X,Wang Q. Alpha-fetoprotein and hepatocellular carcinoma immunity [J]. Can J Gastroenterol Hepatol,2018,2018:9049252.

[40] Donati M,Brancato G,Donati A. Clinical biomarkers in hepatocellular carcinoma(HCC)[J]. Front Biosci (Schol Ed),2010,2:571–577.

[41] Sterling RK,Jeffers L,Gordon F,et al. Utility of lens culinaris agglutinin-reactive fraction of alpha-fetoprotein and des-gamma-carboxy prothrombin,alone or in combination,as biomarkers for hepatocellular carcinoma [J]. Clin Gastroenterol Hepatol,2009,7(1):104–113.

[42] Huang SM,Wu YL. Clinical value of detecting serum GP73 and related indexes of liver fibrosis levels in patients with hepatitis B cirrhosis [J]. Journal of Modern Laboratory Medicine,2014,10(6):142–144. [黄书明,吴玉兰. 乙型肝炎肝硬化患者血清 GP 73 和相关指标的检测及其临床应用价值分析 [J]. 现代检验医学杂志,2014,10(6):142–144.]

[43] Giannelli G,Antonaci S. New frontiers in biomarkers for hepatocellular carcinoma [J]. Dig Liver Dis,2006,38(11):854–859.

[44] Xia Y,Zhang Y,Shen M,et al. Golgi protein 73 and its diagnostic value in liver diseases [J]. Cell Prolif,2019,52(2):e12538.

[45] Choi JY,Jung SW,Kim HY,et al. Diagnostic value of AFP-L3 and PIVKA-Ⅱ in hepatocellular carcinoma according to total-AFP [J]. World J Gastroenterol,2013,19(3):339–346.

[46] Svobodova S,Karlikova M,Topolcan O,et al. PIVKA-Ⅱ as a potential new biomarker for hepatocellular carcinoma–a pilot study [J]. In Vivo (Athens,Greece),2018,32(6):1551–1554.

[47] Omata M,Cheng AL,Kokudo N,et al. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma:a 2017 update[J]. Hepatol Int,2017,11(4):

317–370.

[48] Kudo M,Izumi N,Kokudo N,et al. Management of hepatocellular carcinoma in Japan:consensus-based clinical practice guidelines proposed by the Japan Society of Hepatology(JSH) 2010 Updated Version[J]. Dig Dis,2011,29(3):339–364.

[49] Tan Y,Ge G,Pan T,et al. A serum microRNA panel as potential biomarkers for hepatocellular carcinoma related with hepatitis B virus[J]. PLoS One,2014,9(9):e107986.

[50] Zhou J,Yu L,Gao X,et al. Plasma microRNA panel to diagnose hepatitis B virus-related hepatocellular carcinoma[J]. J Clin Oncol,2011,29(36):4781–4788.

[51] Lin XJ,Chong Y,Guo ZW,et al. A serum microRNA classifier for early detection of hepatocellular carcinoma:a multicentre,retrospective,longitudinal biomarker identification study with a nested case-control study [J]. Lancet Oncol,2015,16(7):804–815.

[52] Hao X,Luo H,Krawczyk M,et al. DNA methylation markers for diagnosis and prognosis of common cancers [J]. Proc Natl Acad Sci U S A,2017,114(28):7414–7419.

[53] Xu RH,Wei W,Krawczyk M,et al. Circulating tumour DNA methylation markers for diagnosis and prognosis of hepatocellular carcinoma[J]. Nat Mater,2017,16(11):1155–1161.

[54] Trinchet JC,Chaffaut C,Bourcier V,et al. Ultrasonographic surveillance of hepatocellular carcinoma in cirrhosis:a randomized trial comparing 3- and 6-month periodicities [J]. Hepatology,2011,54(6):1987–1997.

[55] Wang J H,Chang K C,Kee K M,et al. Hepatocellular carcinoma surveillance at 4- vs. 12-month intervals for patients with chronic viral hepatitis:a randomized study in community[J]. Am J Gastroenterol,2013,108(3):416–424.

[56] Santi V,Trevisani F,Gramenzi A,et al. Semiannual surveillance is superior to annual surveillance for the detection of early hepatocellular carcinoma and patient survival[J]. J Hepatol,2010,53(2):291–297.

[57] Andersson KL,Salomon JA,Goldie SJ,et al. Cost effectiveness of alternative surveillance strategies for hepatocellular carcinoma in patients with cirrhosis[J]. Clin Gastroenterol Hepatol,2008,6(12):1418–1424.

[58] Dong ZW. Cancer screening,early detection and treatment technical program [M]. Beijing:People's Medical Publishing House,2009.154–185. [董志伟. 中国癌症筛查及早诊早治技术方案[M]. 北京:人民卫生出版社,2009.154–185.]

[59] Chen JG,Zhang YH,Zhu J,et al. Early diagnosis and early treatment for liver cancer in Qidong:survival of patients and effectiveness of screening [J]. Chinese Journal of Oncology,2017,39(12):946–951. [陈建国,张永辉,朱健,等. 启东肝癌的早诊早治及筛查效果评价[J]. 中华肿瘤杂志,2017,39(12):946–951.]

[60] Zhang BH,Yang BH,Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma[J]. J Cancer Res Clin Oncol,2004,130(7):417–422.

[61] Chen JG,Parkin D,Chen QG,et al. Screening for liver cancer:results of a randomised controlled trial in Qidong,China[J]. J Med Screen,2003,10(4):204–209.

[62] Kansagara D,Papa KJ,Pasha AS,et al. Screening for hepatocellular carcinoma in chronic liver disease:a systematic review[J]. Ann Intern Med,2014,161(4):261–269.

[63] Yeh YP,Hu TH,Cho PY,et al. Evaluation of abdominal ultrasonography mass screening for hepatocellular carcinoma in Taiwan [J]. Hepatology (Baltimore,Md.),2014,59(5):1840–1849.

[64] Chen THH,Chen CJ,Yen MF,et al. Ultrasound screening and risk factors for death from hepatocellular carcinoma in a high risk group in Taiwan[J]. Int J Cancer,2002,98(2):257–261.

[65] Ji M,Liu Z,Chang ET,et al. Mass screening for liver cancer:results from a demonstration screening project in Zhongshan City,China[J]. Sci Rep,2018,8(1):12787.

[66] Singal AG,Pillai A,Tiro J. Early detection,curative treatment,and survival rates for hepatocellular carcinoma surveillance in patients with cirrhosis:a meta-analysis[J]. PLoS Med,2014,11(4):e1001624.

[67] Mcmahon BJ,Bulkow L,Harpster A,et al. Screening for hepatocellular carcinoma in Alaska natives infected with chronic hepatitis B:a 16-year population-based study[J]. Hepatology,2000,32(4):842–846.

[68] Kemp W,Pianko S,Nguyen S,et al. Survival in hepatocellular carcinoma:impact of screening and etiology of liver disease[J]. J Gastroenterol Hepatol,2005,20(6):873–881.

[69] Tanaka H,Nouso K,Kobashi H,et al. Surveillance of hepatocellular carcinoma in patients with hepatitis C virus infection may improve patient survival [J]. Liver Int,2006,26(5):543–551.

[70] Zhang BH,Yang BH,Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma[J]. J Cancer Res Clin Oncol,2004,130(7):417–422.

[71] El-Serag HB,Kramer JR,Chen GJ,et al. Effectiveness of AFP and ultrasound tests on hepatocellular carcinoma mortality in HCV-infected patients in the USA [J]. Gut,2011,60(7):992.