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Review article: Available modalities for screening and imaging diagnosis of hepatocellular carcinoma—Current gaps and challenges

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Summary

Background: Hepatocellular carcinoma (HCC) incidence and mortality continue to rise worldwide. Society guidelines recommend HCC screening for patients with chronic hepatitis B (CHB) or cirrhosis. Unfortunately, HCC screening rates remain relatively low, and the performance characteristics of current screening modalities are suboptimal.

Aim: The aim of the study was to discuss the current state of HCC screening and imaging diagnosis utilising standard and emerging imaging modalities in addition to outlining areas of need and ongoing study.

Methods: A review of the field was performed combining literature searches and expert opinion.

Results: The development of the Liver Imaging Reporting and Data System (LI-RADS version 2018) algorithms have advanced and standardised the imaging diagnosis of HCC. While guidelines recommend US for HCC screening, the sensitivity of ultrasound is highly variable for the detection of early-stage HCC with sensitivity reports ranging from 40% to 80%. Biomarker-based scores such as GALAD and alternative imaging modalities such as abbreviated MRI are promising tools to improve HCC early detection. Patients with non-alcoholic fatty liver disease (NAFLD) and patients hepatitis C (HCV) who have achieved sustained virologic response (SVR) can present a clinical dilemma regarding the need for HCC screening. Biomarkers and elastography can aid in identification of individuals at high risk for HCC in these populations.

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AUTHOR CONTRIBUTIONS

Abbey Barnard Giustini: Writing –original draft (lead); writing –review and editing (equal). **George N. Ioannou:** Writing –review and editing (equal). **Claude Sirlin:** Writing –review and editing (equal). **Rohit Loomba:** Conceptualization (lead); supervision (lead); writing –review and editing (equal). All authors approved the final version of the manuscript.

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Conclusions: The LI-RADS system has standardised the imaging interpretation and diagnosis of HCC. Work remains regarding screening in special populations and optimization of screening modalities.

1 | INTRODUCTION

Despite advancements in the treatment of viral hepatitis, the incidence of hepatocellular carcinoma (HCC) has risen significantly over recent decades making it one of the most common cancers worldwide.[1] In the United States the incidence of liver cancer, of which 75%–90% is HCC, has more than tripled since 1980.[2] While rates in men have stabilised, incidence continues to rise in women.[2] These data are taken in light of the ongoing COVID-19 pandemic which may limit or influence both data collection and patient behaviour patterns making recent trends difficult to accurately report and interpret. Globally, chronic hepatitis B (CHB) accounts for the majority of HCC despite the demonstrated efficacy of newborn vaccination programmes. For example, a study in Thailand found the standardised incidence rate of HCC in nonvaccinated children older than age 10 was 0.88 per million compared with 0.07 per million in vaccinated children.[3] Patients with cirrhosis from all aetiologies have a very high risk of HCC with an incidence estimated at 2%–4% per year.[4] American Association for the Study of Liver Disease (AASLD) guidelines recommend HCC screening in all patients with cirrhosis and at-risk individuals with CHB.[5] The delayed identification of HCC and the discovery of advanced malignancy is associated with limited treatment options and poor outcomes. Conversely, the detection of HCC at early stage as a result of effective screening can result in potentially curative treatments and excellent outcomes. This review aims to outline available screening modalities as well as key gaps in care and knowledge while highlighting emerging data and areas for future research and growth.

2 | CURRENT RECOMMENDATIONS FOR HCC SCREENING

AASLD guidelines recommend screening with ultrasound with or without alpha-fetoprotein (AFP), every 6 months in select patients with CHB and all patients with cirrhosis (except those with Child's C cirrhosis who are not transplant candidates).[5] This recommendation is supported by a randomised control trial of approximately 18,000 patients in China, which demonstrated a 37% reduction in HCC-related mortality in screened patients and 38 pooled observational studies reporting improved 3 year survival in patients with cirrhosis diagnosed as compared to patients with cirrhosis with no prior screening.[5–7] However, the majority of patients in that study had CHB and the percentage with cirrhosis was not reported. Given the absence of randomised trials of screening in Western populations where aetiologies such as hepatitis C and non-alcoholic fatty liver disease are more prevalent, and where most patients in surveillance programmes have cirrhosis, there remains some debate regarding the true impact of screening on overall survival.

In practice, ultrasound is an operator-dependent modality influenced by body habitus, which can lead to limited or inconclusive studies for the purposes of HCC screening. The limitations of ultrasound visualisation have been codified in the US LI-RADS Algorithm to assist in communication and clinical decision making.[8] This scoring system includes three

visualisation categories: A reflects minimal or no limitations in visualisation; B indicates the limitations of the study may obscure small masses; and C is consistent with severe limitations which lowers the sensitivity of the study for focal liver lesions.[8] A score of A or B is typically considered acceptable for screening. However, repeated studies with visualisation score B may warrant assessment with an alternative modality. A visualisation score of C is insufficient for screening and another imaging modality should be used going forward. Observational studies have reported an increased chance of inadequate ultrasound quality in overweight or obese patients, with up to 1 in 5 ultrasound examinations being of insufficient quality for HCC screening.[9,10] Such findings are of particular concern given the increased prevalence of non-alcoholic fatty liver disease (NAFLD).[11] A recent prospective multicentre study of patients with NAFLD cirrhosis who underwent contemporaneous ultrasound and abbreviated MRI with gadoxetic acid found more than one third of patients had severe limitations in ultrasound screening.[12]

Despite the limitations of ultrasound, given the high cost and relatively limited availability of computed tomography (CT) and magnetic resonance imaging (MRI), these modalities are not currently recommended as first line for HCC screening. At this time abbreviated MRI (AMRI) protocols are emerging as a promising modality for initial and ongoing screening in HCC with the potential for improved diagnostic accuracy relative to ultrasound with lower cost and time burden as compared to complete contrast-enhanced multiphasic MRI examinations.[13] For example, one currently utilised AMRI protocol consists of T2-weighted single shot fast spin echo (SSFSE) and gadoxetic acid-enhanced hepatobiliary phase T1-weighted images; in a retrospective dual-centre study simulating this AMRI protocol the per-patient sensitivity of the AMRI without diffusion weight imaging (DWI) was 82.6%.[13] Per-patient sensitivity for the detection of HCC with an AMRI examination was similar to the reported sensitivity for the complete study with gadoxetic acid.[13] Additionally, the aforementioned prospective study in patients with NASH cirrhosis with a similar AMRI protocol found only one-sixth of patients had severe visualisation limitation with AMRI as compared to the one-third of patients with ultrasound.[12] Prospective studies are ongoing to further evaluate diagnostic accuracy and cost-effectiveness of AMRI in patients meeting criteria for HCC screening. Other AMRI protocols, including some that focus on dynamic contrast enhancement with extracellular agents and others that focus on unenhanced MRI, have also been proposed but have not been as extensively studied yet.

3 | IMAGING DIAGNOSIS OF HCC

3.1 | CT/MRI LI-RADS

If a screening test is positive and/or if HCC is suspected based on an imaging test performed for unrelated reasons, call-back multiphasic CT or multiphasic MRI is recommended. MRI can be performed with extracellular contrast agents or with hepatobiliary contrast agents such as gadoxetic acid.[14] Hepatobiliary contrast agents not only enhance the blood and interstitium but also are taken up by normal hepatocytes via cell membrane transporters. Most HCCs have reduced expression of these transporters and appear hypointense during the hepatobiliary phase.[14,15] Altered membrane transporter expression by HCCs provide an additional mechanism for the detection of these tumours when using hepatobiliary agents.

The CT/MRI Liver Imaging Reporting and Data System (LI-RADS) is a standardised system for the CT-or MRI-based diagnosis and staging of HCC in patients with cirrhosis or CHB without cirrhosis.[14] The LI-RADS algorithm does not apply to patients with vascular causes of cirrhosis such as Budd–Chiari syndrome given the association between these conditions and hypervascular benign liver lesions.[14] This system allows for standardised assessment of lesions and diagnosis of HCC without lesion biopsy in a significant proportion of cases (Figure 1, Table 1). The most recent iteration of LI-RADS (v2018) has been incorporated into the AASLD clinical practice guidance and it is supported and endorsed by the American College of Radiology (ACR).[14] LI-RADS v2018 has increased sensitivity for definite HCC relative to OPTN criteria and LI-RADS v2017, but has similar high specificity.[16,17] It has also been shown to increase inter-reader agreement for imaging features and lesion categorisation.[18]

The LI-RADS algorithm applies a decision tree, diagnostic table, ancillary features and tie-breaking rules to categorise observations detected on surveillance tests or discovered incidentally. Assuming tumour in vein, benign observations such as haemangiomas and arterioportal shunts and observations with targetoid appearance (i.e. imaging features characteristic of non-HCC malignancy) have been excluded, the diagnostic table classifies remaining observations as shown in Figure 2.[19] Observations that are ≥10 mm and have non-rim arterial phase hyperenhancement can be categorised as definite HCC (LR-5) if they have the right combination of additional major features (Figure 3).[19] The majority of patients with suspicious lesions on ultrasound will proceed to CT or MRI for further evaluation, but in clinical scenarios where a patient is not a candidate for these modalities, contrast-enhanced ultrasound (CEUS) offers an additional mode of HCC diagnosis. CEUS is a specialised form of ultrasound (US) performed with an intravenous injection of microbubble contrast agents which are not nephrotoxic. CEUS can be utilised for both the diagnosis of and imaging guidance for ablative treatment of HCC.[20] CEUS can be used in patients who are not candidates for other contrast-enhanced studies, to assess observations previously seen on CT or MRI and is particularly useful in characterising arterial phase hyperenhancement for observations in which a mistiming of contrast on prior studies is suspected.[20] Analogous to CT/MRI LI-RADS, CEUS LI-RADS is a standardised system for the CEUS-based diagnosis of HCC.

The LI-RADS algorithms offer comprehensive and rigorous standardisation of the imaging diagnosis of HCC and continue to evolve as new clinical data and technologies emerge. Integration of LI-RADS into practice guidelines and broad implementation are promising avenues of quality assurance in the arena of HCC screening and surveillance.

4 | GAPS IN QUALIT Y

4.1 | Rates of screening

Despite clear and established recommendations, rates of HCC screening remain low. A retrospective analysis of a single safety net hospital showed that only 74.8% of patients received initial screening within 1 year of cirrhosis diagnosis and among those who completed this initial screening only 47.6% underwent a second surveillance exam within a year.[21] Another study reviewed the electronic medical record for patients with cirrhosis

at 11 Veterans Health Administration facilities and found a little less than half of patients underwent at least one HCC screening test (serum AFP or ultrasound) over a 6 month period.[22] This is notably higher than comparable studies in non-veteran populations. For example, the pooled estimate of surveillance in a recent systemic review and meta-analysis was only 24%.[22,23] Poor retention in screening programmes is multifactorial. Patient-reported barriers include the challenge of scheduling an examination, cost of testing and transportation.[24] Notably, studies have shown that screening is significantly more likely to occur when patients are established with and seen regularly by a gastroenterology or hepatology provider.[25] This finding highlights the potential for provider education initiatives and electronic medical record-based reminder systems and pathways to improve screening rates in the future. Perceptions about the low sensitivity of ultrasound may contribute to non-adherence, suggesting that the development of more accurate surveillance approaches might improve compliance.

5 | FUTURE DIRECTIONS

5.1 | Biomarkers

Ultrasound is the current recommended screening modality for HCC and its sensitivity for HCC detection has been reported to range between 40% and 80%.[26] Notably, A large meta-analysis of 32 studies comprising 13,367 patients found the sensitivity of ultrasound alone for the detection of early-stage disease HCC was only 47%.[27] In addition to the investigation of alternative imaging modalities, another area of great interest and study involves the integration of biomarkers with ultrasound to optimise sensitivity. One such serum biomarker model is the hepatocellular carcinoma early detection screening algorithm (HES) which was developed in the department of Veterans Affairs utilising data from the hepatitis C virus clinical case registry and later validated in a cohort of veterans with cirrhosis of any aetiology.[28,29] This algorithm uses current AFP level, rate of AFP change, age, level of alanine aminotransferase and platelet count.[29] At a specificity of 90% the sensitivity of the HES algorithm was superior to AFP alone at 52.6%.[29] While this is a modest improvement this algorithm garnered attention as it is based on laboratory parameters readily available to the majority of practitioners and therefore is further supported by the likely ease of implementation into clinical practice.

Another serum biomarker-based model is the GALAD score which incorporates age, AFP, AFP-L3% and Des-gamma-carboxy-prothrombin (DCP) to predict the probability of a patient having HCC.[30] A cohort study in the United States found that the area under the ROC curve (AUC) of the GALAD score for HCC detection was superior to ultrasound alone (0.95 vs. 0.82 [95% confidence interval (CI): 0.93–97])[31] This study also proposed the GALADUS score, which combines the GALAD score and ultrasound, and was superior to ultrasound and GALAD score alone for the detection of HCC (AUC of 0.98 [95% CI: 0.96–0.99]). While some of the inputs, such as DCP, may not be familiar to all providers, this biomarker-based tool offers ease of implementation and a signal towards increased early HCC detection.

With multiple potential tools and models in development, ongoing study and validation is needed. In a prospective phase 3 cohort study examining AFP, AFP-L3%, DCP, GALAD

and the HES algorithm for early HCC detection GALAD offered increased sensitivity, but with a notable increase in false positives as compared to any of the individual biomarkers examined.[32] Ultimately there were no significant differences in the AUROC between GALAD, HES, AFP-L3% and DCP.[32] Future studies will need to assess the cost-effectiveness of GALAD and account for patient-and healthcare-level burdens and costs.

Liquid biopsy, which broadly speaking refers to the analysis of nucleic acids, subcellular structures and tumour cells in the circulation, has dramatically changed standard practice in a number of malignancies allowing for rapid molecular diagnosis of malignancy and treatment guidance.[33] Work has been ongoing to identify potential tumour-specific biomarkers in HCC. A novel multitarget HCC blood test (mt-HBT) combines information from 3 methylation markers, AFP and patient sex to assess for the presence of HCC.[34] In clinical validation mt-HBT showed 88% overall sensitivity and 82% early-stage sensitivity (as defined by Barcelona Clinic Liver Cancer stages 0 and A) at 87% specificity.[34] These results indicate that mt-HBT is a promising tool for early HCC detection. Further validation studies are ongoing.

Further prospective studies across diverse populations are needed to guide use of biomarkers in HCC detection. In addition to the examples provided above there are numerous other biomarker candidates and models at varying stages of development and validation.[35] As data emerges consideration should be given to ease of implementation, costs and the potential for sequential application of models and biomarkers to optimise the detection of early HCC.[35] Data are rapidly emerging in this area. Changes to patient care and standard practice are likely on the horizon.

6 | SPECIAL POPUL ATIONS

6.1 | Screening in NAFLD

Another area of interest in the realm of HCC screening is the consideration of enrolment of additional at-risk populations into screening programmes. One such population is patients with NAFLD. Recent estimates project that between 21% and 33% of the population is affected by NAFLD with those numbers expected to rise in coming years.[11] A recent American Gastroenterological Association (AGA) clinical practice update on screening for HCC in patients with NAFLD recommends consideration of HCC screening in patients where non-invasive markers suggest advanced fibrosis or cirrhosis.[36] Liver biopsy remains the gold standard for assessment of fibrosis, but given the large burden of NAFLD it is not reasonable to utilise this invasive measure for all patients who warrant risk stratification. Consequently, these guidelines recommend combining at least two non-invasive testing modalities which broadly speaking can be classified as point-of-care testing, specialised blood tests (such as Fibrosure) and imaging-based tests[37] One such modality is the FIB-4 score which is calculated based on age, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and platelet count. A retrospective cohort study analysing the data from 130 facilities in the Veterans Health Administration showed that a FIB-4 score of >2.67 was associated with an increased risk of HCC in both patients with an established diagnosis of cirrhosis and those without a diagnosis of advanced liver disease.[38] It further showed that the risk for HCC in patients with NAFLD and low FIB-4 was low (0.004% per

year).[38] In imaging-based testing the threshold of 16.1 kPa for vibration-controlled transient elastography (VCTE) and 5 kPa for magnetic resonance elastography (MRE) have been proposed to qualify individuals for HCC screening with a target of 90% specificity for advanced fibrosis and cirrhosis.[37,39] Prospective multicentre validation of these thresholds is needed.

Another emerging tool for risk stratification is the polygenic risk score (PRS) of hepatic fat content.[40] This research demonstrated that the impact of genetic risk variants on fibrosis is proportional to that on hepatic fat confirming its role as a driver of hepatic disease. Additional work supports the causal role of hepatic fat accumulation in hepatic carcinogenesis and suggests that PRS may be useful as a tool for identifying individuals with high genetic risk for HCC.[41]

Prospective studies are needed to both optimise the implementation of the risk stratification tools available to qualify an individual for screening and to gather further data on the clinical impact of HCC screening programmes in the setting of NAFLD without cirrhosis.

6.2 | Screening in patients with eradicated hepatitis C (HCV)

Direct acting anti-viral agents (DAAs) revolutionised the treatment of HCV by providing highly effective medications with favourable safety profiles.[42] A systematic review of 30 observational studies examining the risk of HCC in patients treated for HCV who both achieved sustained virologic response (SVR) and those who did not found that the relative risk of HCC in persons with advanced liver disease decreased with the achievement of SVR (1.05% pooled incidence per person-year of HCC versus 3.30% per person-year).[43] However, despite this improved risk profile data at this time support ongoing screening for patients with cirrhosis who have achieved SVR. For example, a study of approximately 29,000 patients in the Veterans Affairs healthcare system with cirrhosis who were treated with DAAs and achieved SVR found that even at seven years following eradication of HCV HCC risk exceeded the 1% per year threshold for screening.[44]

The persistence of HCC risk following eradication of HCV is likely multifactorial, but the slow resolution of fibrosis following SVR likely accounts for a significant component of the residual HCC risk.[45] As such, similar to the risk stratification of NAFLD patients outlined above, there is interest in the utilisation of non-invasive markers of fibrosis to guide decisions regarding HCC screening following SVR. As it stands, no single marker has been universally adopted. Potential candidates include FIB-4, which is readily available and validated for fibrosis assessment in patients with HCV.[46] An elevated FIB-4 score ≥3.25 was shown to be a strong predictor of HCC risk in both patients with and without cirrhosis and could be considered an acceptable threshold to qualify patients for screening.[47] Imaging-based fibrosis assessment is another widely available tool which could be applied to risk stratification of patients who have achieved SVR. For example, a prospective single-centre study of approximately 530 patients with HCV treated with DAAs who underwent MRE prior to treatment found that an MRE value of ≥4.5 kPa was associated with HCC development.[48] Further studies are needed to validate this threshold across varied populations prior to clinical use.

Another proposed strategy is to directly estimate HCC risk rather than utilise tools which estimate fibrosis stage as a surrogate for HCC risk. One such tool is the aMAP score developed to estimate HCC risk using age, gender, albumin, bilirubin and platelet counts and was validated in international cohorts.[49] The score ranges from 0 to 100 and a cut-off of 60 was determined to best discriminate high-risk patients (5-year cumulative incidence of HCC of 19.9%).[49] Despite this tool's strong performance, provider knowledge of and easy access to such a tool are potential barriers to its implementation. Another tool for HCC risk estimation developed using data from patients undergoing HCV treatment at Veterans Health Administration facilities eliminates some of this impediment by making their calculator readily available at www.hccrisk.com and providing a 3 year HCC risk estimate after the input of selected demographic and laboratory data.[50]

As with NAFLD, the population of patients with a history of HCV who have now achieved SVR is not a small one and as such there must be consideration of both the cost and resource utilisation of not only risk stratification tools, but ultimately the HCC screening strategy selected for these patients as well (AMRI, US, etc). The ideal clinical workflow could allow for a sufficiently accurate assessment of HCC risk as to prioritise high risk patients to the most accurate screening modality.[45] Further studies are needed to validate HCC risk tools in large populations, but as it stands now the participation of individuals with advanced fibrosis warrants consideration.

6.3 | Screening in patient with CHB with complete viral suppression

HCC is a significant cause of morbidity and mortality in patients with CHB occurring even in the absence of cirrhosis.[51] Nucleoside and nucleotide analogues allow for effective viral suppression resulting in fibrosis regression and reduction in liver-related mortality.[52] Treatment with this group of medications has been shown to reduce, but not eliminate, HCC risk.[53] In current practice, patients continue to undergo screening following complete viral suppression due to this persistent risk. Multiple tools and scoring systems have been developed to assess HCC risk in the setting of CHB, such as CU-HCC, GAG-HCC and REACH-B, but these tools were found to have unsatisfactory performance in Caucasian patients and those on treatment with entecavir.[54] The PAGE-B score was developed based on age, gender and platelets in a Caucasian patient population on treatment with entecavir and tenofovir disoproxil fumarate and was later modified with the addition of albumin to create the mPAGE-B score.[54,55] Both the PAGE-B and mPAGE-B scores have subsequently been validated in a large cohort study in Hong Kong.[56] The AUROC (95% confidence interval) for the prediction of HCC at 5 years was 0.77 (0.76–0.78) for PAGE-B and 0.80 (0.79–0.81).[56] Approximately 29% of patients were classified as having low HCC risk by either the PAGE-B or mPAGE-B scores and this classification reached a negative predictive value (NPV) of 99.5% to exclude patients without HCC development by 5 years.[56] However, this did not hold for patients with CHB and cirrhosis and even those with low risk scores had an estimated annual risk of HCC greater than 1%.[56] These scores offer significant promise as they are readily calculable with standard laboratory data and do not require additional inputs such as elastography. Further validation of these scores is needed across diverse populations and ideally should include patients treated with tenofovir alafenamide as well.

While at this time no guidelines endorse their routine implementation this may be altered in the future with further study.

7 | CONCLUSIONS

HCC remains a pressing clinical issue, and gaps exist both regarding implementation of current screening guidelines and optimization of screening strategies (Figure 4). Advances in knowledge and technical capability offer promise for better tools for screening and risk stratification. As it stands now those caring for patients with advanced liver disease should ensure that those who traditionally fall into the cohort for HCC screening receive that screening in a timely manner and confirm that imaging is of sufficient quality. In addition, there should be consideration of expanded screening for certain patients with cured HCV and NAFLD (Table 2). Awareness of current best practices among providers and attention paid to new developments will be essential to ensure optimised screening of at-risk patients. Based on the emerging data highlighted in this review, significant growth is anticipated.

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CONFLICT OF INTEREST STATEMENT

Dr. Rohit Loomba serves as a consultant for Anylam/Regeneron, Amgen, Arrowhead Pharmaceuticals, AstraZeneca, Bristol-Myer Squibb, CohBar, Eli Lilly, Galmed, Gilead, Glympse bio, Inipharm, Intercept, Ionis, Janssen Inc., Madrigal, Metacrine, Inc., NGM Biopharmaceuticals, Novartis, Novo Nordisk, Pfizer, Sagimet, 89 bio, and Viking Therapeutics. In addition, his institution has received grant support from Allergan, Astrazeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly, Galectin Therapeutics, Galmed Pharmaceuticals, Genfit, Gilead, Intercept, Inventiva, Janssen, Madrigal Pharmaceuticals, Merck, NGM Biopharmaceuticals, Pfizer and Siemens. He is also co-founder of Liponexus, Inc. Dr. Sirlin reports research grants from ACR, Bayer, Foundation of NIH, GE, Gilead, Pfizer, Philips, Siemens; lab service agreements with Enata, Gilead, ICON, Intercept, Nusirt, Shire, Synageva, Takeda; institutional consulting for BMS, Exact Sicences, IBM-Watson, Pfizer; Personal consulting for Altimmune Ascelia Pharma, Blade, Boehringer, Epigenomics, and Guerbet; receipet of royalities and/or honoraria from Medscape and Wolters Kluwer; ownership of stock options in Livivos; unpaid advisory board position in Quantix Bio. Dr. Sirlin serves as Chief Medical Officer for Livivos (unsalaried position with stock options), an appointment approved by his university. Doctors Barnard Giustini and Ioannou have nothing to disclose.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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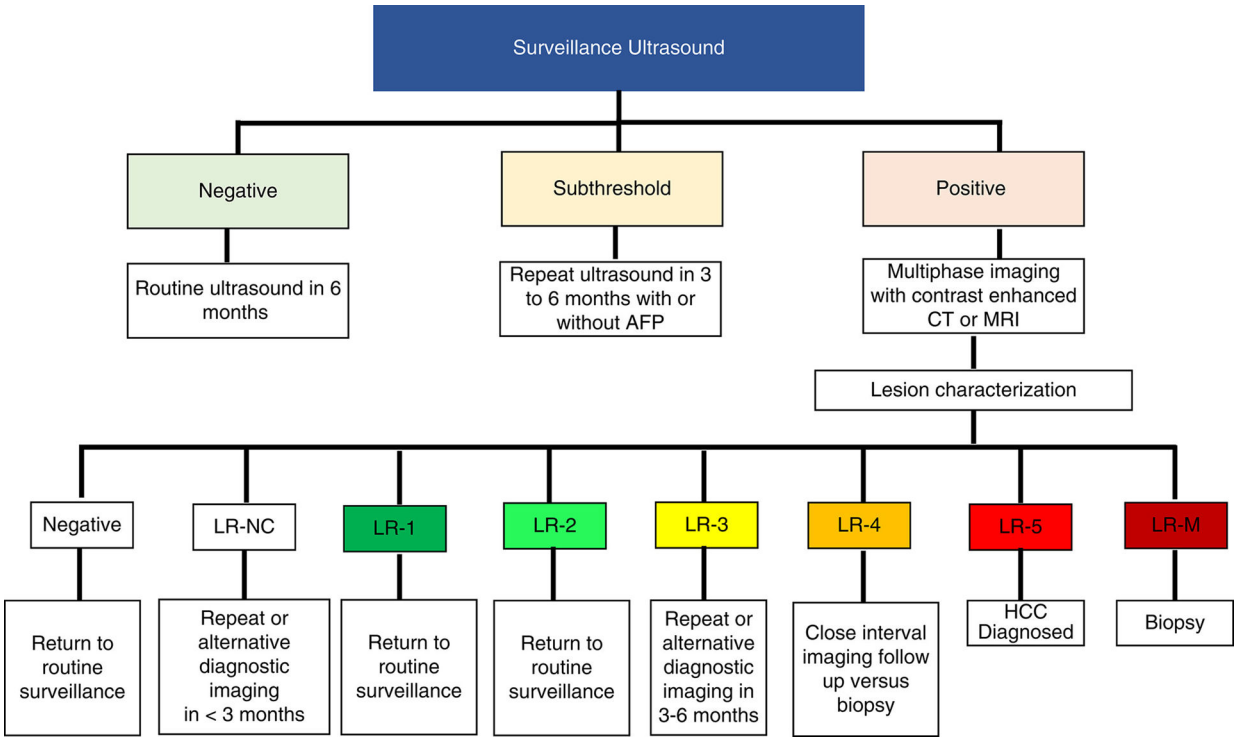

FIGURE 1.

Adapted from Marrero JA. Hepatology. 2018;68 (2):723–50. Surveillance ultrasound is recommended for all patients with cirrhosis and select patients with CHB and can be completed with or without AFP. A negative ultrasound is defined by the presence of no lesions or definitely benign lesions. A subthreshold exam demonstrates a lesion less than 10 mm and warrants closer follow-up. A positive ultrasound is defined by the detection of a greater than 10 mm lesion and warrants further imaging. Diagnostic imaging should be read by a radiologist experienced in liver imaging and reviewed by a multidisciplinary board as indicated based on lesion classification.

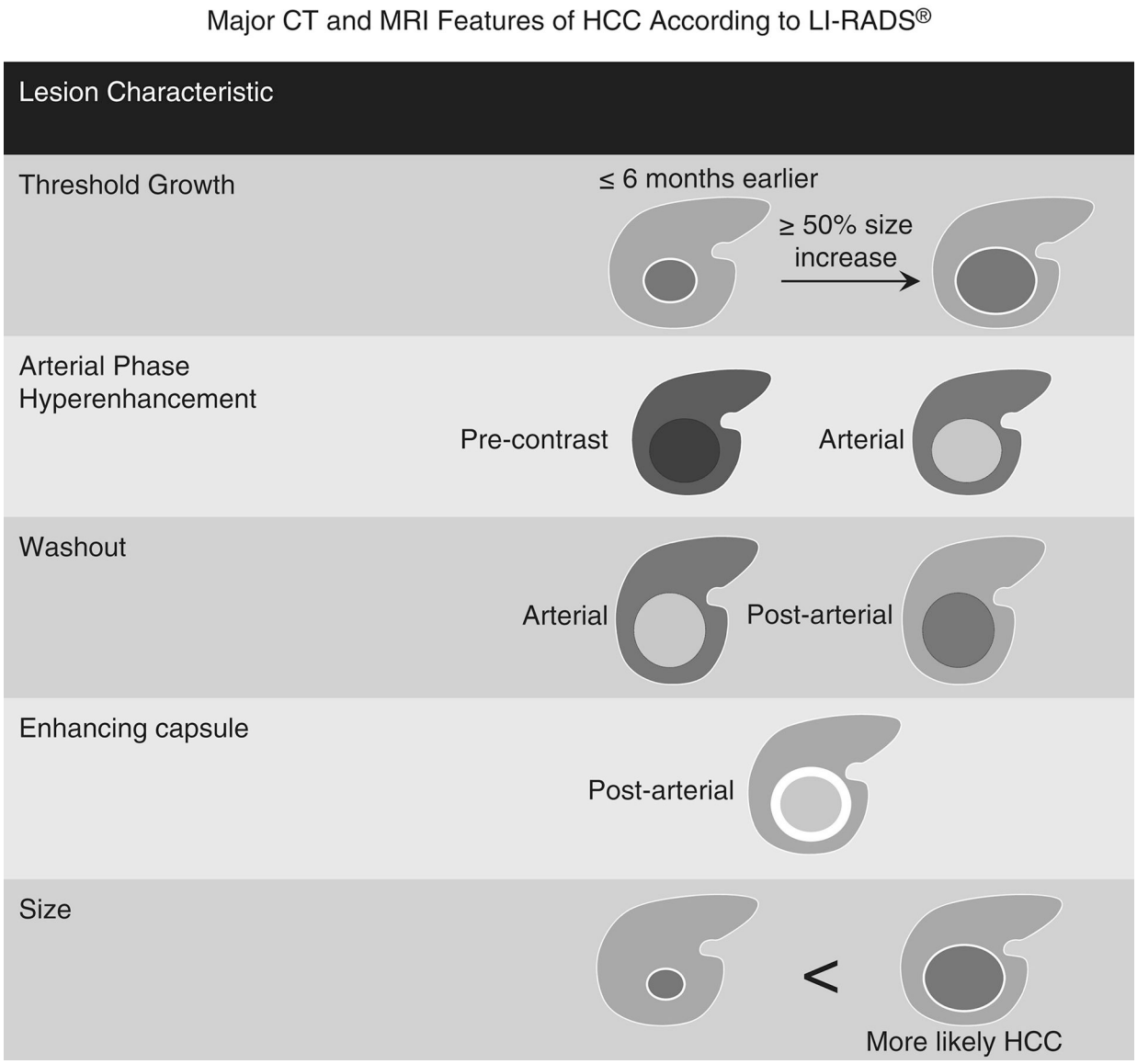

FIGURE 2.

Lesion characteristics concerning for HCC. The following are a selection of characteristics concerning for HCC and are utilised in the LI-RADS classification system. Threshold growth is an increase in size of 50% or more within 6 months time during follow-up imaging. Arterial phase hyperenhancement (APHE) is non-rim arterial hyperenhancement of a lesion which is greater than the enhancement of the surrounding liver. Rim enhancement is not a feature of HCC. Non-peripheral washout is a decrease in attenuation or intensity from earlier to later phase, resulting in hypoenhancement in the portal venous or delayed phase. Capsule is a smooth, uniform border surrounding all or most of an observation. Size refers to the concept that a large lesion has a greater chance of being an HCC than a small lesion.

Arterial Phase Hyperenhancement (APHE)		No APHE		Nonrim APHE		
Observation Size (mm)		< 20	> 20	< 10	10-19	≥ 20
Count additional major features: - Enhancing capsule - Nonperipheral washout - Threshold growth	None	LR-3	LR-3	LR-3	LR-3	LR-4
	One	LR-3	LR-4	LR-4	LR-4 or LR-5*	LR-5
	≥Two	LR-4	LR-4	LR-4	LR-5	LR-5

*Observations in this category are categorized based on an additional major feature:

- LR- 4 if an enhancing capsule is present
- LR- 5 if nonperipheral washout or threshold growth is present

FIGURE 3.

Adapted from LI-RADS® CT/MRI v2018 core document. The LI-RADS algorithm allows for the classification of liver lesions based on observation size, presence of arterial phase hyperenhancement (APHE) and additional major features presuming the absence of features concerning for advanced malignancy or non-hepatocellular carcinoma malignancy such as the presence of tumour in vein.

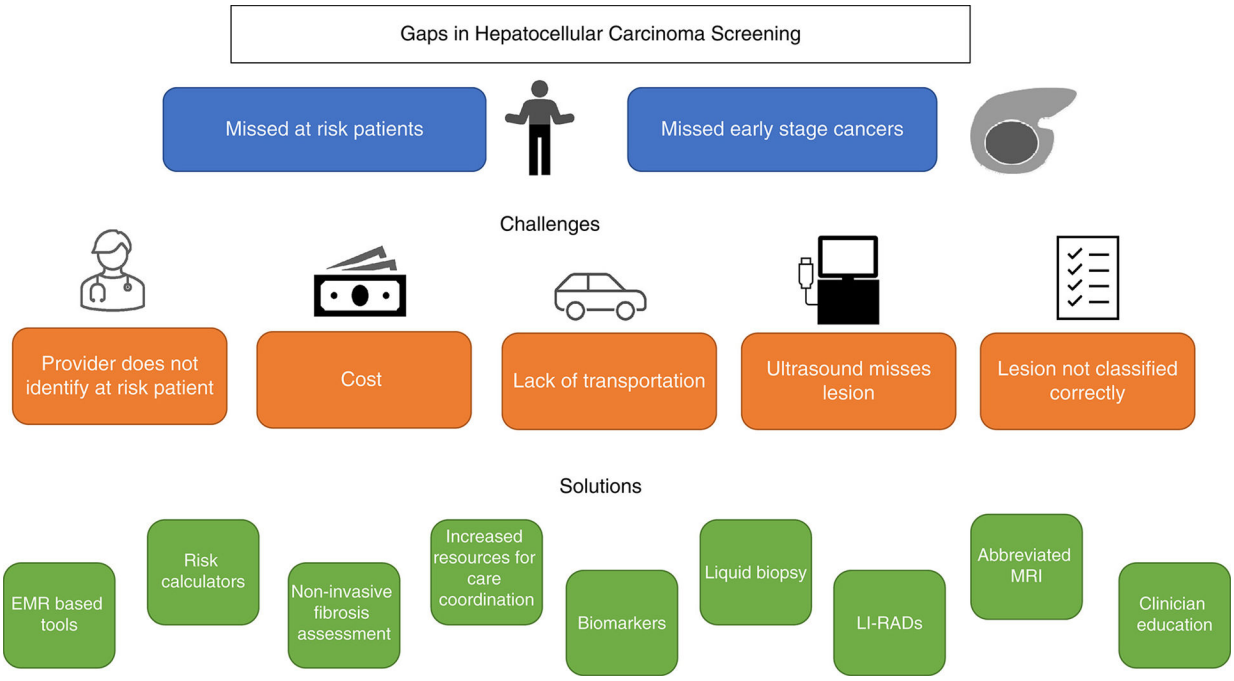

FIGURE 4.

Gaps in Hepatocellular Carcinoma (HCC) Screening. Despite the known benefits of screening for HCC many at-risk patients do not undergo screening. The reason for this is likely multifactorial due to gaps in clinician knowledge regarding who should be referred for screening, cost concerns and lack of transportation. A patient may also undergo recommended screening, but an early lesion may be missed due to suboptimal imaging. There are a number of tools and strategies currently in use and emerging to optimise HCC screening. Electronic medical record (EMR) based reminders, risk calculators and non-invasive fibrosis assessment can help clinicians identify at-risk patients. Biomarkers, liquid biopsy and abbreviated magnetic resonance imaging (MRI) may help identify more early-stage HCCs. The LI-RADS classification system allows for easy identification of suboptimal ultrasound exams and offers clear recommendations for follow-up of liver lesions. Finally, clinician education is also needed to ensure current and emerging strategies are incorporated into practice where they can make a difference for patient care.

Table 1:

LI-RADS categories according to the CT/MRI LI-RADS v2018 system

LR 1	Definitely benign
LR 2	Probably benign
LR 3	Intermediate probability of malignancy
LR 4	Probably HCC
LR 5	Definitely HCC
LR M	Probable or definite malignancy with imaging features that are not specific to HCC
LR TIV	Definite tumour in vein
LR- NC	Observations that cannot be categorised due to image degradation or omission

Note: LI- RADS diagnostic categories reflect the relative probability of benignity, HCC, or overall malignancy. Observations categorised LR-M have high likelihood of being malignant but may not be HCC. These lesions usually require biopsy for further evaluation prior to treatment. The development and implementation of LI-RADS represents a major milestone in HCC screening, but even with this system there remain areas of growth and need for further research.

TABLE 2

Suggested populations for HCC Screening

Populations recommended for screening based on major guidelines	
Patients with chronic hepatitis B	Benefit is uncertain in men younger than 40 and women younger than 50 without cirrhosis or a family history of HCC
Patients with cirrhosis	Except those with Child's C cirrhosis who are not transplant candidates
Additional populations to consider for screening	
Patients with NAFLD and advanced fibrosis	Advanced fibrosis as defined by FIB-4>2.67, VCTE>16.1kPa, or MRE>5kPa
Patients with HCV following SVR with advanced fibrosis and elevated HCC risk	Advanced fibrosis and elevated HCC risk as defined by FIB-4>3.25, aMAP score>60, MRE>4.5kPa, etc.

Note: Guidelines from major societies recommend that patients with chronic hepatitis B and patients with cirrhosis, excluding those with Child's C disease, should undergo routine HCC screening. In addition to these populations, data are emerging that sufficient risk of HCC is present in patients with NAFLD and advanced fibrosis and select patients with HCV following SVR that screening is likely warranted. A number of metrics and scores are available to estimate HCC risk in these populations with varying degrees of clinical use and validation. These tools can be used in addition to clinical presentation and patient preferences to guide the decision to initiate or defer screening.