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REVIEW

Biomarkers *vs* imaging in the early detection of hepatocellular carcinoma and prognosis

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Abstract

Hepatocellular carcinoma (HCC) is the 5th most frequently diagnosed cancer in the world, according to the World Health Organization. The incidence of HCC is between 3/100000 and 78.1/100000, with a high incidence reported in areas with viral hepatitis B and hepatitis C, thus affecting Asia and Africa predominantly. Several international clinical guidelines address HCC diagnosis and are structured according to the geographical area involved. All of these clinical guidelines, however, share a foundation of diagnosis by ultrasound surveillance and contrast imaging techniques, particularly computed tomography, magnetic resonance imaging, and sometimes contrast-enhanced ultrasound. The primary objective of this review was to systematically summarize the recent published studies on the clinical utility of serum biomarkers in the early diagnosis of HCC and for the prognosis of this disease.

Key words: Hepatocellular carcinoma; Biomarkers; Imaging; Ultrasonography; Computed tomography; Magnetic resonance imaging

Core tip: Hepatocellular carcinoma (HCC) is an important cause of morbidity and mortality worldwide. Current HCC screening and diagnostic guidelines are based on imaging techniques-ultrasonography for screening, and dynamic contrast-enhanced computed tomography, magnetic resonance, and ultrasound for diagnosis. The use of biomarkers is promising but the diverse aetiology and complex pathophysiological mechanisms of HCC make it difficult to find an ideal combination. This review systematically summarizes the existing data on the role of biomarkers in early diagnosis and prognosis of HCC, to promote efforts to find alternatives to the imaging investigations which are expensive and not always accepted by patients.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the 5th most frequently diagnosed cancer in the world, according to the World Health Organization (WHO)[1]. The incidence of HCC is between 3/100000 and 78.1/100000, with high incidence reported in areas with viral hepatitis B and hepatitis C, these being represented predominantly by the Asian and African geographic regions[1]. As such, the international clinical guidelines that are currently in use were generated according to the geographical area involved.

For HCC surveillance in general, persons with chronic hepatitis B virus (HBV) infection (HBV DNA level > 2000 IU/mL), HBV-related cirrhosis, family history of HCC or age over 40 years, the WHO guidelines recommend abdominal ultrasound and alpha-fetoprotein (AFP) measurement every 6 mo[2]. The same recommendations are given for patients with hepatitis C virus (HCV)-related cirrhosis[3].

The Canadian guidelines recommend ultrasound surveillance every 6 mo for high-risk groups, including individuals with HBV- or HCV-related cirrhosis, cirrhosis on fatty liver disease, or chronic carriers of HBV, as well as for non-cirrhotic patients[4]. If a liver nodule with a diameter of less than 1 cm is found, ultrasonography (US) will be repeated over 3 mo, in order to assess the increase in diameter or change in characteristics[4]. In the very early stage, the diagnosis could be done with radiologic techniques, such as 4-phase dynamic contrast-enhanced computed tomography (CT) scan or gadolinium-enhanced magnetic resonance imaging (MRI), or biopsy[4]. Contrast-enhanced US (CEUS) has the same sensitivity as dynamic contrast-enhanced CT or MRI in liver nodule diagnosis[4]. For indeterminate liver nodule, biopsy showing cellular characteristics and positive staining for glypican-3, glutamine synthetase, heat shock protein 70 and clathrin heavy chain are necessary[4]. Serum biomarkers such as AFP, AFP-L3 (the fucosylated component of AFP or lens culinaris agglutinin-reactive fraction of AFP) and des-gamma-carboxy prothrombin (DCP) are more useful in late-stage or aggressive HCC than in the early stage of small HCC, mainly because the biomarkers are not highly sensitive[4].

The American Association for the Study of Liver Diseases (commonly known as the AASLD) *guidelines* recommend 6-mo interval surveillance for cirrhotic patients, carried out by US with or without AFP detection[5]. For the HCC diagnostic evaluation, multiphasic CT or multiphasic MRI have similar performance[5]. The contrast agents used are extracellular (giving information about the liver nodule based on blood flow) or hepatobiliary (giving additional information about hepatocellular function)[5]. The selection of imaging method and contrast agent is made based upon the individual patient, MRI contraindications, and institutional factors[5]. In North America, multiphasic CEUS is not widely used, but it can be used for non-invasive HCC diagnosis[5]. If an indeterminate liver nodule has been discovered in a cirrhotic patient, it can be followed by imaging, with an alternative imaging procedure and/or an alternative contrast agent, or biopsy[5]. Large multicentre prospective studies are still needed, however, to identify non-imaging characteristics for predicting HCC progression as accurately as possible[5].

The American College of Gastroenterology (ACG) clinical guidelines recommend CT or MRI when a liver nodule is greater than 1 cm, with acoustic shadow detected by US, when AFP is elevated or rising in the absence of liver nodule, or with clinical suspicion of HCC[6].

For HCC screening, the National Comprehensive Cancer Network guidelines recommend 6-mo interval US for cirrhotic patients of any cause and for chronic hepatitis B patients, with or without AFP detection[7]. If US is inadequate, multiphasic contrast-enhanced CT or MRI are recommended[7].

The Australian guidelines include US and AFP as initial investigations in HCC surveillance[8]. HCC diagnosis is made based on findings from four-phase contrast-enhanced CT, contrast enhanced-MRI, CEUS in selected cases, and finally with PET and liver biopsy[8].

The European Association for the Study of the Liver (EASL) guidelines recommend ultrasonographic surveillance every 6 mo performed by experienced persons on individuals in high-risk populations[9]. In general, the AFP level varies in patients with

HBV- or HCV-related cirrhosis, either during flares of the infection, exacerbation of the cirrhotic state, or HCC progression[9]. For these reasons, AFP could produce false-positive results and is not used in surveillance programs[9]. As a diagnostic test, when added to ultrasound assessment, AFP has good sensitivity (with a 20 ng/mL cut-off) and good specificity (with a 200 ng/mL cut-off)[9]. These values were mostly obtained in patients with viral infection activity but cannot yet support the calculation of a cost-effective ratio for early HCC surveillance programs[9]. As to the clinical utility of the other biomarkers in the diagnosis or prognosis of the disease, they (*i.e.*, ALP-L3, DCP) are not recommended, alone or in combination, for early detection of HCC in surveillance programs[9]. For early diagnosis of HCC, the *EASL guidelines* recommend imaging techniques (multiphasic contrast-enhanced CT, dynamic contrast-enhanced MRI, or CEUS) for liver nodules of more than 1 cm diameter[9]. In small HCC, MRI with hepatobiliary contrast agents (*e.g.*, gadoxetic acid and gadobenate dimeglumine) has higher sensitivity than MRI with extracellular agents[9]. In non-cirrhotic cases, histological and immunohistological tests are used to confirm the HCC diagnosis[9].

The same recommendations are provided by the European Society for Medical Oncology (ESMO), with multiphasic contrast-enhanced CT or MRI for HCC diagnosis and no role for AFP in the diagnostic work-up[10].

The Japan guidelines recommend ultrasound examination with AFP measurement every 3-6 mo[11]. For cirrhotic patients, dynamic CT or dynamic MRI are recommended[11]. The three serum biomarkers AFP, AFP-L3 and DCP are used for definitive diagnosis of HCC or for the subsequent surveillance exams[11]. These biomarkers are also used to estimate the efficacy of treatment in HCC patients who presented elevated levels before treatment[11]. The response to treatment could be occasionally assessed, but with difficulty, by imaging techniques, with the associated changes (*e.g.*, lipiodol deposits, arterioportal shunt) compared to the serum biomarkers[11]. CEUS is recommended for estimating the residual tumours after percutaneous ablation therapy and transcatheter arterial chemoembolization[11].

The Asia-Pacific clinical practice guidelines recommend US only as a screening test and suggest it to not represent a diagnostic test[12]. When the screening test is positive, the diagnosis of HCC is made by dynamic CT, dynamic MRI, or gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced MRI[12]. From among the serum biomarkers, AFP with a level more than 200 ng/mL is used in combination with US in the surveillance programs[12]. Being a marker of necroinflammation and regeneration, AFP is elevated in active hepatitis and cirrhosis in the absence of HCC[12]. For that, in small HCC, AFP is not recommended as a confirmatory test[12]. Its level decreases with improvement of chronic hepatitis B activity and post-treatment with interferon treatment for chronic hepatitis C[12]. AFP-L3 seems to be more useful than AFP alone in differential diagnosis of HCC from benign nodules[12]. The role of DCP (also termed prothrombin induced by vitamin K absence II (PIVKA-II)) is still controversial in diagnostic performance for small HCC, as compared with AFP[12]. Serum glypican-3, as an HCC serum diagnostic biomarker, is also inconsistent[12]. Other serum biomarkers, such as Golgi protein 73 (GP73), osteopontin, microRNAs or circulating free DNA, are not yet applied in clinical practice, mainly due to the heterogeneous results of clinical trials and low cost-benefit[12]. No ideal combination of serum biomarkers has yet been found, as the increase in sensitivity is achieved with decreased specificity[12] (Table 1).

The International guidelines for CEUS recommendations cites dynamic CEUS as capable of evaluating the enhancement patterns of a liver nodule during arterial, portal venous and late phases, with the appearance being similar as that in contrast-enhanced CT and contrast-enhanced MRI[13].

CEUS has advantages over dynamic CT or MRI according to its features of providing a real-time evaluation of the arterial phase, applicability to renal failure patients, and its ability to diagnose malignant or non-malignant portal vein thrombosis, to select one or more nodules for biopsy from multiple nodules with different patterns, to localize small HCC for percutaneous ablation and to assess recurrence[4,13]. The post-vascular phase (also known as the Kupffer phase) can be evaluated with a specific ultrasonographic contrast agent, perfluorobutane, having a hydrogenated egg phospatidyl serine shell[13]. Enhancement defect can better characterize the HCC nodule[13]. Dependence on the operator's experience and a lower visibility of the sub-diaphragmatic segment of the liver, especially in liver steatosis, are the main disadvantages of CEUS[13] (Table 2).

LITERATURE SEARCH

A systematic literature search was carried out in the PubMed, Web of Science Core

Table 1 International guidelines for hepatocellular carcinoma surveillance programs

Guideline	Indications	AFP	Imaging	Period (mo)
WHO	HBV DNA > 2000 UI/mL, HCV cirrhosis	+	US	6
Canadian	Cirrhosis, HBV chronic carriers		US	6
AASLD	Cirrhosis	+/-	US	6
NCCN	Cirrhosis, HBV chronic hepatitis	+/-	US	6
Australian			US	
EASL			US	6
Japan	Cirrhosis	+	US/dynamic CT/MRI	3-6
Asia-Pacific		> 200 ng/mL	US	6

AASLD: American Association for the Study of Liver Diseases; CT: Computed tomography; EASL: European Association for the Study of the Liver; HBV: Hepatitis B virus; HCV: Hepatitis C virus; MRI: Magnetic resonance imaging; NCCN: National Comprehensive Cancer Network; US: Ultrasonography; WHO: World Health Organization.

Collection, Elsevier ScienceDirect and Google Scholar databases for the past 5 years, using the terms "hepatocellular carcinoma", "biomarkers hepatocellular carcinoma", and "imaging hepatocellular carcinoma". A total of 2318 articles and 720 reviews were found. The articles included in the study were limited to English full-text articles and reviews in humans, and excluding case reports or post-specific treatment (*i.e.*, chemotherapy or radiotherapy) studies.

AFP USED IN ALGORITHMS OR IN COMBINATION WITH OTHER BIOMARKERS

Genetic correction

Various authors have attempted to increase AFP sensitivity by different algorithms. The efficiency of serum AFP in primary HCC seems to be improved by genetic correction; for example, using the single-nucleotide polymorphisms rs12506899 and rs2251844, as shown in a Chinese study of elderly patients reported by Wang *et al*[14].

Age, biochemical laboratory tests, serial values of AFP

Tayob *et al*[15] used an algorithm based on patient age, findings of laboratory tests, and serial measurements of AFP levels for improving the rate of HCC detection in HCV-related cirrhosis. When AFP was incorporated in another algorithm along with levels of alanine aminotransferase (ALT), alkaline phosphatase, age and sex, the rate of HCC detection in HCV, HBV and non-viral liver disease was significantly enhanced, as shown by Wang *et al*[16].

AFP and DCP (PIVKA II)

Yu *et al*[17] found DCP sensitivity and specificity for HBV-related HCC to be greater than AFP. In that study, when DCP and AFP were used together as diagnostic biomarkers for HCC, their sensitivity and specificity were even greater. Chen *et al*[18] found that the various prediction algorithms including AFP and DCP had a higher efficacy for early HCC diagnosis in patients with liver cirrhosis. Fu *et al*[19] analysed the combination of DCP and AFP as biomarkers for primary HCC diagnosis, finding higher effects than with each biomarker alone. Qin *et al*[20] showed that a panel test comprised of AFP (cut-off of 10 ng/mL), DCP (cut-off of 4 ng/mL) and dickkopf-1 (cut-off of 2 ng/mL) had both a high sensitivity and specificity, superior to each biomarker alone. However, future studies are needed to assess the role of this panel in detecting early HCC and the cut-off levels for different stages of HCC[20].

In a meta-analysis, Chen *et al*[21] found that DCP had a better accuracy than AFP for detection of HCC, regardless of the tumour diameter, the patients' ethnicity (American, European, Asian, or African), or the aetiology of HCC (HBV-related or mixed). For the diagnosis of HCC associated with alcoholic and non-alcoholic fatty liver disease, AFP and DCP appeared to be the best combination of biomarkers in the study by Beale *et al*[22]. At a level of 15 ng/mL, AFP alone had a good sensitivity and a specificity of 100%[22]. Increasing AFP values during the course of liver disease should prompt a careful surveillance, while increased DCP levels prompt suspicion of larger tumours[22]. In monitoring of the evolution of hepatic cirrhosis associated with fatty liver disease, glypican-3, squamous cell carcinoma antigen-I, and follistatin have no benefit, according to this study[22].

Table 2 International guidelines for hepatocellular carcinoma diagnosis

Guideline	Liver nodule US	Biomarkers	Indications for biomarkers
Canadian	CT/MRI/CEUS	AFP, AFP-L3, DCP	Late stage/aggressive
AASLD	CT/MRI		
ACG	CT/MRI		
NCCN	CT/MRI		
Australian	CT/MRI/CEUS: Selected case		
EASL	CT/MRI/CEUS		
ESMO	CT/MRI		
Japan	CT/MRI	AFP, AFP-L3, DCP	Definitive diagnosis, efficacy of treatment
Asia-Pacific	CT/MRI/CEUS		

AFP: Alpha-fetoprotein; AFP-L3: Alpha-fetoprotein L3; AASLD: American Association for the Study of Liver Diseases; CEUS: Contrast-enhanced computed tomography; CT: Computed tomography; DCP: Des-gamma-carboxyprothrombin; EASL: European Association for the Study of the Liver; ESMO: European Society for Medical Oncology; MRI: Magnetic resonance imaging; NCCN: National Comprehensive Cancer Network; US: Ultrasonography.

AFP, AFP-L3, and DCP (PIVKA II)

Yu *et al*[23] reported that in early HCC, AFP-L3 has the best specificity and GP73 has the best sensitivity. The use of four combined biomarkers (AFP, AFP-L3, DCP, and GP73) in neural network models was shown to be capable of differentiating early HCC from liver cirrhosis[23]. Li *et al*[24] demonstrated that a panel test of AFP, AFP-L3 and PIVKA II with the GALAD scoring algorithm is better for early diagnosis of HCC than any of the biomarkers used alone. The utility of the triple combination of the biomarkers was also demonstrated by other authors, including Gao *et al*[25], Caviglia *et al*[26], Best *et al*[27], and Berhane *et al*[28]. Optimal follow-up was analysed by Oeda *et al*[29], as an independent factor of receipt of curative treatment. Wongjarupong *et al*[30] revealed an association between AFP, AFP-L3, DCP and tumour size, to predict the recurrence after liver transplant. Best *et al*[27] studied patients with HCC of different aetiology (*i.e.*, viral infection, and alcoholic and non-alcoholic steatohepatitis) and found an increased specificity for AFP (cut-off of 20 ng/mL) in non-viral HCC; AFP-L3 had an increased sensitivity in non-viral HCC, and DCP had an increased specificity in viral HCC. Combination of the three biomarkers improved the sensitivity, and the use of GALAD scores increased the specificity, including for early HCC diagnosis.

AFP and AFP-L3

Li *et al*[31] analysed a combination of high-level AFP, AFP-L3 and AFP-L3 to AFP ratio and ALT, as predictive factors for HCC in HBV cirrhotic patients, while GP73 level decreased after development of HCC. Kim *et al*[32] used multiple reaction monitoring-mass spectrometry and found serum AFP-L3 as the lower limit and producing less false-negative results.

AFP and osteopontin

Duarte-Salles *et al*[33] suggested a combination of osteopontin and AFP as the best predictors for HBV-related HCC. Ge *et al*[34] showed that osteopontin in combination with AFP and dickkopf-1 have an increased sensitivity in early diagnosis of HBV-related HCC; osteopontin alone had a lower specificity, being increased in chronic HBV hepatitis and liver cirrhosis.

AFP and neutrophil-to lymphocyte ratio

Xing *et al*[35] suggested combinations of AFP and neutrophil-to-lymphocyte ratio for diagnosis of HBV- and HCV-related HCC. Hu *et al*[36] identified AFP, neutrophil-to-lymphocyte ratio, tumour size, and tumour number were independent predictors of microvascular invasion in HCC, associated with HBV and HCV infection.

AFP and serum human endothelial cell-specific molecule-1

Youssef *et al*[37] revealed that serum level of human endothelial cell-specific molecule-1 (cut-off of 2967 pg/mL) had a high sensitivity and specificity in HCV-related HCC patients. In combination with AFP and vascular endothelial growth factor, it was also found to be a predictive factor for mortality.

Serum thioredoxin

Li *et al*[38] found a higher sensitivity and specificity for serum thioredoxin (cut-off level 20.5 ng/mL) in detecting early HCC compared to those for AFP; when the two were combined the sensitivity increased.

AFP, α-L-fucosidase (AFU), and 5'-nucleotidase (5'-NT)

In a small number of patients with primary HCC, Junna *et al*[39] found the combination of AFU, 5'-NT and AFP to have significantly elevated levels (*vs* a control group).

OTHER BIOMARKERS FOR EARLY DETECTION OF HCC IN AFP-NEGATIVE PATIENTS

Although GPC3, GP73, osteopontin, micro (mi)RNAs, MDK, DKK1, and VEGF play roles in the diagnosis, prognosis and treatment of HCC, Song *et al*[40] and Chiba *et al*[41] revealed the need for further studies before widespread use in clinical practice. In a study of cirrhotic patients with HBV-related HCC, Shu *et al*[42] showed levels of AFP-L3 and GP-3 to be insignificantly different from those in the control group, but the fucosylated PON1 level was significantly increased. For cirrhotic patients with low-level AFP (< 20 ng/mL), an algorithm based on clinical characteristics, AFP and fucosylated kininogen was proposed by Wang *et al*[43]. In a study of hepatitis B surface antigen (HBsAg)-positive patients, Guo *et al*[44] found the combination of AFP and serum CD14 (AFP/CD14 cut-off of 0.197 ng/mL) to have higher sensitivity and specificity in early diagnosis of HCC. Kim *et al*[45] shows that fibronectin can differentiate HCC from cirrhosis. Chen *et al*[46] found soluble intercellular adhesion molecule-1 to be highly associated with HCC development in patients with HBV, HCV, non-alcoholic fatty liver disease, and alcoholic or cryptogenic liver disease. In a small study, Badr *et al*[47] found the serum calcium channel α2δ1 subunit (cut-off of 14.22 ng/mL) to have a high sensitivity and specificity, suggesting its potential as a novel biomarker in early detection of HCC in HCV cirrhotic patients. Wang *et al*[48] revealed an increased specificity, but a low sensitivity, of serum autoantibodies to nucleophosmin 1, 14-3-3zeta and mouse double minute 2 homolog proteins. Tayaka *et al*[49] proposed the von Willebrand factor antigen as a predictive biomarker for HCC development in HBV and HCV chronic hepatitis. Finally, several cytokines with significantly increased levels in HCC (*e.g.*, IL-1β, IL-6, IL-10, IL-17A, IL-22, and IL-250) and others with lower levels (*e.g.*, IL-4 and IL-33) in peripheral blood were shown by *Shen et al*[50] to be specific for HCC.

No biomarker to date has been shown to have high accuracy in the early detection of HCC; although, some may have clinical utility in the near future, as revealed by Tsuchiya *et al*[51]. While it has been shown that combinations of biomarkers or algorithms that add other clinical variables increase sensitivity and specificity, randomized clinical trials are required to validate the optimal combinations, especially in early detection of HCC, as suggested by Tsuchiya *et al*[51], Khattab *et al*[52] and Lou *et al*[53].

DCP (PIVKA-II)

In a meta-analysis, Zhu *et al*[54] demonstrated that DCP had moderate accuracy in early HCC diagnosis. Moreover, the results indicated DCP level may be different depending on ethnicity, possibly due to the predominantly different aetiology of HCC (alcoholic cirrhosis *vs* HBV and HCV chronic hepatitis) between Caucasians and Asians[54].

MiRNAs

MiRNAs are non-coding, endogenous, small RNAs, released in the case of liver cell damage into peripheral blood. Although there are multiple published studies, we cannot yet establish a unitary vision of the best combination of miRNAs for early diagnosis of HCC. This may be due, at least in part, to the different aetiologies of HCC in various geographic areas and possibly to genetic polymorphisms. Some authors have reported miRNA as a single test or in combination with other biomarkers/biochemical tests useful in the early diagnosis of HCC. Xu *et al*[55] reported that serum exosomal hnRNPH1 mRNA (cut-off of 0.670) had a high sensitivity and specificity for HCC, suggesting its potential as an HCC diagnostic biomarker in regions of high HBV prevalence. In combination with AFP, these values were improved. However, the authors of this study were not able to compare RNA levels in patients with active

HBV infection *vs* inactive, compensated *vs* decompensated liver cirrhosis, or various stages of fibrosis[55].

In a small study, Balkan *et al*[56] found no difference in levels of miR-122 and miR-192 between the HCC group (mostly patients with HBV-related disease) and the control group (non-alcoholic fatty liver disease patients). In contrast, the miR-26 serum level was much lower in the HCC patients. Long *et al*[57] reported a higher sensitivity and specificity for miR-88 in the whole blood *vs* AFP for detection of early HCC, also HBV-related. Shi *et al*[58] found an association of mi-RNA-106b with HCC for early detection, but further trails are needed to determine the threshold value. Liu *et al*[59] reported miRNA-125b, AFP and tumour size to be predictors of microvascular invasion in patients with HCC, prior to surgery. Serum level of miR-4463 was reported by Hu *et al*[60] to be significantly higher in HCC patients, no matter the sex of the patients, the size of the nodule, the stage of the HCC, the pathological type, or the values of the other serum factor tests (*i.e.*, ALT, aspartate aminotransferase, total bilirubin, and HBsAg status). In that study the highest level of miRNAs was found in the group of patients with the lowest level of AFP and shorter survival time[60].

Other authors have reported combinations of miRNAs useful in the early diagnosis of HCC. As reported by An *et al*[61], miR-122 in combination with miR-375, miR-10a, and miR-423 could be used for diagnosis and prognosis of HCC. Jiang *et al*[62] reported a panel with miR-10b, miR-106b, miR-181a as biomarkers applicable to screening for HCC in Chinese patients. Xue *et al*[63] reported the success of another panel composed of eight miRNAs (miR-122, miR-125b, miR-145, miR-192, miR-194, miR-29a, miR-17-5p, miR-106a) with significantly increased levels in serum for patients with HCC (mostly associated with HBV infection). Liu *et al*[64] studied a combination of high serum miR-21 and mi-R106b and low serum mi-R224 levels and found a high sensitivity and specificity for HCC compared with cirrhotic levels, predominantly HBV-related. In a meta-analysis, Liao *et al*[65] revealed that serum miR-21 could be used as a co-biomarker in early detection of HCC, due to its high sensitivity and specificity. In another meta-analysis, by Ding *et al*[66], multiple serum miRNAs (miR-21, miR-199, and miR-122) had a relatively high accuracy in HCC diagnosis. Xu *et al*[67] showed that serum levels of miRNA-25, miRNA-375 and let-7f can play a role in diagnosis of HCC. Finally, high levels of serum exosomal miR-122, miR-148a and AFP were studied by Wang *et al*[68] and found to be adequate for HCC diagnosis and screening programs (Table 3).

In comparison to the predominant HCV aetiology, the HBV-related HCC has a different profile of altered miRNA expression. Mohamed *et al*[69] studied miR-23a and found a high sensitivity for HCC, mostly for HCV-related cases. Other authors have reported on a panel of miRNAs useful in the early diagnosis of HCV-related HCC. Motawi *et al*[70] reported a combination of serum miR-19a, miR-146a, miR-192 and miR-195 with increased accuracy in early detection of HCV-related HCC. Amr *et al*[71] reported miR-122 and miR-224 as early diagnostic serum biomarkers in HCV-related HCC. Elemeery *et al*[72] found that a panel of miRNAs composed of miR-214-5p, miR-375, miR-125b and miR-1269 had an increased sensitivity for the early detection of HCV-related HCC. Serum miR-939 and miR-595 were identified by Fornari *et al*[73] as independent factors for HCC, mostly involving HCV-related cases. In that same study, the serum level of miR-519d was found to be correlated with the tissue level of miR-519d in HCC[73].

Xue *et al*[63] reported miR-106a to be an independent factor of overall survival and prognosis, fitting with its role in promotion of tumorigenesis. Zhuang *et al*[74] detected serum miR-128-2 in most of the patients with HBV-associated HCC. Results from a study by Zhu *et al*[75] suggested the potential of miR-192-5p and miR-29a-3p as biomarkers for progression of HBV-related HCC and survival, with an inverse relationship. Similarly, the results from a study suggested miR-23a as a prognostic biomarker.

In a systematic review, Klingenberg *et al*[76] concluded that non-coding RNAs [miRNA and long non-coding (lnc) RNA] can be used for early diagnosis in HCC, due to high sensitivity and specificity; however, most of the studies analysed had included cases with only one or two HCC aetiologies. If an HBV-related HCC panel of miRNAs (including miR-122 and miR-21) was to be studied for its diagnostic biomarker potential, the miRNAs should also be investigated for their potential in diagnosis of HCC associated with non-alcoholic fatty liver disease, alcohol or HCV infection in large trials with the specific group patients, as demonstrated by Schütte *et al*[77].

Zhang *et al*[78] considered the multiple origins of miRNAs, the lack of standardized protocols for pro-analytical manipulation of samples in research, the physiologic processing that would occur after the point of analysis, the unknown miRNA binding proteins, and the lack of existing large studies on patients and control populations to support any single or combination of miRNAs in a panel for clinical application for the detection and prognosis of patients with HCC. Likewise, Loosen *et al*[79] cited the

Table 3 MicroRNAs in hepatocellular carcinoma

miRNA	Hepatitis virus	Ref.
For early diagnosis		
exosomal hnRNPH1 miR	HBV	Xu *et al*[55]
miR-26	HBV	Balkan *et al*[56]
miR-88	HBV	Long *et al*[57]
mi-R-106b		Shi *et al*[58]
miR-125b		Liu *et al*[59]
miR-4463		Hu *et al*[60]
miR-10a, miR-122, miR-375, miR-423	HBV	An *et al*[61]
miR-10b, miR-106b, miR-181a	HBV	Jiang *et al*[62]
miR-17-5p, miR-29a, miR-106a, miR-122, miR-125b, miR-145, miR-192, miR-194	HBV	Xue *et al*[63]
miR-21, mi-R106b, mi-R224	HBV	Liu *et al*[64]
miR-21		Liao *et al*[65]
miR-21, miR-122, miR-199		Ding *et al*[66]
miR-25, miR-375, let-7f		Xu *et al*[67]
miR-122, miR-148a, AFP	HBV	Wang *et al*[68]
miRNA-23a	HCV	Mohamed *et al*[69]
miR-19a, miR-146a, miR-192, and miR-195	HCV	Motawi *et al*[70]
miR-122, miR-224	HCV	Amr *et al*[71]
miR-125b, miR-214-5p, miR-375, miR-1269	HCV	Elemeery *et al*[72]
miR-595, miR-939	HCV	Fornari *et al*[73]
For overall survival and prognosis		
miR-106a	HBV	Xue *et al*[63]
miR-128-2	HBV	Zhuang *et al*[74]
miR-192-5p and miR-29a-3p	HBV	Zhu *et al*[75]
miR-23a	HCV	Mohamed *et al*[69]

HBV: Hepatitis B virus; HCV: Hepatitis C virus.

need for standardization of sample collection, analysis, and data normalization and quantification methods to generate findings to support the inclusion of miRNAs in a diagnostic algorithm applied in clinical practice.

LncRNAs

LncRNAs are non-protein-coding transcripts with more than 200 nucleotides. Yuan *et al*[80] showed that, among the circulating lncRNAs, LINC00152, RP11-160H22.5 and XLOC014172 in combination with AFP could be predictive biomarkers for HBV-related HCC. Wang *et al*[81] found the lncRNAs uc001ncr and AX800134 to have high accuracy in detection of HBV-related HCC, especially in the early stage and when the level of AFP is lower than 400 ng/mL. Tang *et al*[82] found three lncRNAs RP11–160H22.5, XLOC_014172 and LOC149086, that can predict the occurrence of HBV-related HCC. Zheng *et al*[83] showed that high expression of serum UCA I is associated with high-grade HCC and advanced TNM stage, suggesting the potential of this factor as a biomarker for screening. In another study, Xu *et al*[84] demonstrated that ENSG00000258332.1 (cut-off of 1.345) and LINC00635 (cut-off of 1.690) had high sensitivity and specificity for HBV-related HCC. When these biomarkers were combined with AFP level higher than 20 ng/mL, both the sensitivity and the sensibility were increased (Table 4).

A meta-analysis by Chen *et al*[85] found that a panel of serum or plasma lncRNAs including LINC00152, RP11-160H22.5, XLOC014172, LOC149086 or HULC, Linc00152 or uc001ncr, AX800134 or PVT1, and uc002mbe.2 had a higher accuracy in HCC than any single lncRNA or in tissue samples. In that meta-analysis, the sensitivity and the specificity of the collective lncRNA biomarkers were both higher for Asian patients than for African patients[85]. In another meta-analysis, Hao *et al*[86] identified multiple factors that influenced the accuracy of lncRNAs in detecting HCC. However, the various aetiologies around the world (*i.e.*, HCV infection in Africa and Egypt, and HBV infection in Asia) may underlie the observation of plasma lncRNAs having a lower accuracy than serum lncRNAs[86].

Table 4 LncRNAs in hepatocellular carcinoma

LncRNA	Hepatitis virus	Ref.
For early diagnosis		
LINC00152, RP11-160H22.5 and XLOC014172	HBV	Yuan *et al*[80]
uc001ncr and AX800134	HBV	Wang *et al*[81]
RP11–160H22.5, XLOC_014172 and LOC149086	HBV	Tang *et al*[82]
UCA I	HBV	Zheng *et al*[83]
ENSG00000258332.1, LINC00635	HBV	Xu *et al*[84]
LINC00152, RP11-160H22.5, XLOC014172, LOC149086 or HULC, Linc00152 or uc001ncr, AX800134 or PVT1, uc002mbe.2		Chen *et al*[85]
Predictors for poor prognosis		
BANCR		Qin *et al*[88]
XLOC_014172 and LOC149086	HBV	Tang *et al*[82]
UCA I	HBV	Zheng *et al*[83]

HBV: Hepatitis B virus; HCV: Hepatitis C virus; lncRNA: Long non-coding RNA.

Zheng *et al*[87] reported poor rates of survival (1.25-fold increased risk) and recurrence-free survival (1.66-fold increased risk) in patients with higher levels of lncRNAs, supporting the proposal of these factors to serve as predictive biomarkers for HCC prognosis. Indeed, Qin *et al*[88] found high levels of the plasma lnc-RNA BANCR in HCC patients and determined a correlation with poor prognosis. In the study by Tang *et al*[82], the secondary increase of lncRNAs XLOC_014172 and LOC149086 following surgical treatment was found to be predictive of metastasis. Finally, serum UCA I was proposed by Zheng *et al*[83] as another biomarker for prognostic evaluation.

PLASMA METABOLITES

HCC is characterized by aerobic glycolysis, increased consumption of glucose, and high levels of lactate. This type of metabolism persists immediately following surgery or transcatheter arterial chemoembolization, as demonstrated by Chen *et al*[89]. Kim *et al*[90] studied the molecular changes produced by alteration in the energy metabolism pathways that underlie the metabolomic and proteomic observations, in order to better determine their practical application in the early detection of HCC. The study by Di Poto *et al*[91] supported a proposal for the combination of plasma metabolites with other co-variates, such as AFP, in early detection of HCC in cirrhotic patients. Saito *et al*[92] studied the serum metabolomic profile in patients with HBV-related HCC compared to that in patients with HCV-related HCC, and found distinctions, especially for glutamic acid, methionine, and gamma-Glu-Gly-Gly. Similarly, the type of HBV or HCV infection and the metabolic profile of the patient have important roles in establishing the metabolomic panel as diagnostic and prognostic markers in HCC, as shown by Fitian *et al*[93]. Finally, Ferrin *et al*[94] studied the potential protein biomarkers in HCV-alcoholic patients and identified the complement component 4a as an independent predictor of HCC.

Kimhofer *et al*[95] analysed numerous studies of metabonomic and proteomic biomarkers in a comprehensive review. The metabonomic biomarkers that have been studied are bile acids, lysophosphatidylcholines, free fatty acids, carnitine and energy metabolism-related products, but the best panel of these for early detection of HCC need to be validated before inclusion in future guidelines[95]. Finally, Guo *et al*[96] showed that although there are technological advances, the study of metabolomics, particularly for that of HCC, is still in its infancy.

SERUM LIPIDS

Passos-Castilho *et al*[97] proposed seven lipids detected by spectrometry as predictive of HCV-related HCC, with high sensitivity and moderate specificity. In a later study, Passos-Castilho *et al*[98] proposed four lipids as independent predictor factors of HBV-related HCC in cirrhotic patients, with moderate sensitivity and specificity.

SERUM BIOMARKERS FOR PREDICTION PROGRESSION OF DISEASE, POOR PROGNOSIS, AND RECURRENCE

Margetts *et al*[99] found a neutrophil-to-lymphocyte ratio of > 3.15 to be associated with poor survival. In addition, the Systemic Immune-Inflammation Index score was found to be strongly correlated with tumour size. High neutrophil-to-lymphocyte ratio was also proposed by Zheng *et al*[100] as a predictive biomarker of poor survival and poor recurrence-free survival in HCC patients before treatment. That study also found the high neutrophil-to-lymphocyte ratio as well as the platelet-to-lymphocyte ratio to be independent predictive factors for survival and recurrence in HCC patients with curative and palliative treatment. Goyal *et al*[101] proposed the red blood cell distribution width useful when to be incorporated in a prognostic panel of other inflammatory biomarkers for outcomes after HCC surgery. Serum cartilage oligomeric matrix protein and interleukin-6 have been studied by Van Hees *et al*[102] and shown to be predictive factors of HBV-related HCC, but large-scale studies are needed to validate them for use in current practice. In another study, by Hong *et al*[103], autoantibodies against tumour-associated antigens appeared to be more useful in the prognosis of HCC than in its early diagnosis; again, large studies are needed to clarify their roles in the various stages of HCC. Finally, Sun *et al*[104] determined that the circulating tumour cells assay is not useful for HCC detection when used as the sole biomarker; however, it did show promise as a predictor of poor prognosis.

The serum antibodies anti-HSP 70 and anti-Eno-1 were shown by Yu *et al*[105] to be predictive of microvascular invasion in HBV-related HCC prior to surgical treatment, with anti-Eno-1 having a better sensitivity and specificity.

IMAGING DIAGNOSIS

Kuo *et al*[106] reported a higher cost-effectiveness ratio for ultrasound screening compared to bimodal biomarkers (AFP and US) for early detection of HCC in endemic areas. However, this assessment cannot be universally valid, especially if screening is performed in patients with cirrhosis and without specialized and well-trained staff. A meta-analysis by Hanna *et al*[107] showed that CEUS has the same sensitivity as contrast-enhanced CT or gadolinium-enhanced MRI in diagnosis of HCC and that it is useful for supplementary characterization of the liver nodules detected by US.

Although dynamic CEUS has an important role in the diagnosis and characterization of small liver tumours, the ultrasonographic differential diagnosis between HCC and intrahepatic cholangiocellular carcinoma is difficult, sometimes having the same hypervascularization and washout pattern, as shown by Van Beers *et al*[108]. This does not happen with contrast-enhanced MRI or CT performed with small-molecular-weight agents, for both intravascular and extravascular extracellular space distribution[107]. Westwood *et al*[109] performed a systematic review to review imaging techniques and found that the sulphur hexafluoride microbubble used as contrast agent in US seems to have the same performance as contrast-enhanced-CT or MRI for diagnosis of focal liver lesions. However, it is necessary to standardize dynamic CEUS and generate clear criteria for comparing the three methods in the same patient[108,109]. Yao *et al*[110] proposed radiomic analysis in multi-modal US to determine the best to obtain a better differential diagnosis between benign and malign liver tumours, with a good prediction of microvascular invasion and Ki-67 and PD-1 expression.

The best sensitivity (85.6%) and positive predictive value (94.2%) in the imaging diagnosis of HCC has been reported for MRI with gadoxetate as the contrast agent, according to meta-analysis findings from Hanna *et al*[107]. In that study, the MRI with gadoxetate rates were followed by MRI with other contrast agents, contrast enhanced-CT, and US without contrast agent respectively. Although CEUS seems to have high sensitivity and positive predictive value, reference standards are required for proper comparison of the three contrast-enhanced imaging methods (MRI, CT, and US)[107]. In a comprehensive review, Ippolito *et al*[111] revealed the differences in contrast agents used in dynamic contrast-enhanced MRI perfusion according to application by different researchers and depending upon the intended purpose. For diagnosing and evaluating early HCC characteristics, gadobenate-dimeglumine or gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid (Gd-EOB-DTPA) is recommended[111]. For prognosticating the disease, gadodiamide is recommended[111]. For investigating treatment response, Gd-EOB-DTPA, dadobenate-dimeglumine, gadopentetate-dimeglumine or gadodiamide are recommended[111].

According to European Society of Gastrointestinal and Abdominal Radiology (commonly known as ESGAR) consensus, Neri *et al*[112] revealed that MRI with Gd-

EOB-DTPA as the contrast agent is the best technique for characterization of focal lesions with diameter equal to or greater than 10 mm in a cirrhotic liver. The dual renal and hepatocyte elimination of Gd-EOB-DTPA makes it useful as a contrast agent for both perfusion imaging in the early phase and for hepatocyte imaging in the late phase[112]. Through dynamic contrast-enhanced MRI with Gd-EOB-DTPA, morphological and functional data can be obtained[112]. These features are particularly useful for HCC in cirrhotic liver, in late hepatic arterial phase (*i.e.*, hepatic artery and portal vein enhancement) and hepatobiliary phase (*i.e.*, delayed by reduced hepatic function)[112]. If MRI combines Gd-EOB-DTPA as a contrast agent with a diffusion weighted imaging technique, additional qualitative and quantitative data can be obtained on the degree of HCC differentiation, microvascular invasion, or response to treatment[111].

Functional MRI (*i.e.*, magnetic resonance elastography, diffusion-weighted MRI, or T1-weighted dynamic contrast-enhanced MRI) provides additional quantitative and qualitative information that is extremely useful both in HCC early diagnosis and in prognosis and response to treatment; these techniques are expected to find application on a large scale in clinical practice in the near future[111,112].

Tanabe *et al*[113] showed that the time interval between imaging investigations should be determined according to the initial LI-RADS staging. Because ultrasonographic nodules smaller than 2 cm in cirrhotic patients may be included in MRI investigations as initial LI-RADS stages and subsequently determined to be early HCC, Darnell *et al*[114] proposed an active work-up, including biopsy, for optimal HCC management. Yang *et al*[115] analysed some methods as dual-input two-compartment pharmacokinetic models of dynamic contrast-enhanced MRI to determine which could better predict microvascular characteristics of HCC. The dual-input extended Tofts model could better measure the extravascular extracellular space volume ratio, while the dual-input two-compartment exchange model could better predict the microvascular permeability. These data will be very useful for personalized treatment but need standardization and further large trials.

Kavanaugh *et al*[116] suggested that the complex cellular mechanisms involved in HCC growth determine a higher detection rate of small tumours by (4S)-4-(3-[^{18}F]fluoropropyl)-L-glutamic acid (^{18}F-FSPG) positron emission tomography (PET)-CT compared to 11C-acetate PET-CT; the former does not reach 100%, however, as not all HCCs express the x_c-transporter (gene symbol SLC7A11). Cho *et al*[117] revealed the utility of fluorine-18 fluorodeoxyglucose (^{18}F-FDG) PET-CT in early or intermediate HCC, in management of the disease (*i.e.*, hepatic resection or liver transplant), but it was found to not be useful in very early-stage HCC without extrahepatic metastases. Of note, accumulation of the ^{18}F-FDG radiotracer in inflammatory liver lesions is one of the limitations of this method for its use in the diagnosis of a hepatic nodule as HCC[117].

CONCLUSION

All clinical guidelines for diagnosis of HCC are based on ultrasound surveillance and contrast imaging techniques (*i.e.*, CT, MRI, and sometimes CEUS). Although there have been important advances in our understanding of the roles of various biomarkers in certain stages of the disease, especially in combinations, large studies involving certain population groups are needed before biomarkers can be introduced into clinical practice on a large scale. The different predominant aetiologies of certain geographical areas (*i.e.*, high incidence of HBV, HCV, alcoholic and non-alcoholic fatty liver disease, cryptogenic disease) make it difficult to find a unique combination of biomarkers for the diagnosis of HCC. Nonetheless, imaging techniques still play a leading role in both HCC surveillance and diagnosis.

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