

World Journal of *Gastroenterology*

World J Gastroenterol 2021 October 7; 27(37): 6161-6347



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INDEXING/ABSTRACTING

The WJG is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, and Scopus. The 2021 edition of Journal Citation Report® cites the 2020 impact factor (IF) for WJG as 5.742; Journal Citation Indicator: 0.79; IF without journal self cites: 5.590; 5-year IF: 5.044; Ranking: 28 among 92 journals in gastroenterology and hepatology; and Quartile category: Q2. The WJG's CiteScore for 2020 is 6.9 and Scopus CiteScore rank 2020: Gastroenterology is 19/136.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Ying-Yi Yuan*, Production Department Director: *Xiang Li*, Editorial Office Director: *Ze-Mao Gong*.

NAME OF JOURNAL

World Journal of Gastroenterology

ISSN

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE

October 1, 1995

FREQUENCY

Weekly

EDITORS-IN-CHIEF

Andrzej S Tarnawski, Subrata Ghosh

EDITORIAL BOARD MEMBERS

<http://www.wjgnet.com/1007-9327/editorialboard.htm>

PUBLICATION DATE

October 7, 2021

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INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

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<https://www.wjgnet.com/bpg/GerInfo/287>

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<https://www.wjgnet.com/bpg/gerinfo/240>

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<https://www.wjgnet.com/bpg/gerinfo/208>

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<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Surveillance for hepatocellular carcinoma at the community level: Easier said than done

Paolo Del Poggio, Marzio Mazzoleni, Sergio Lazzaroni, Andrea D'Alessio

ORCID number: Paolo Del Poggio 0000-0002-9387-8909; Marzio Mazzoleni 0000-0003-4295-0904; Sergio Lazzaroni 0000-0002-7369-8476; Andrea D'Alessio 0000-0002-6797-0410.

Author contributions: All authors equally contributed to this paper with conception and design of the study, literature review, drafting, critical revision and editing; they all have approved the final version.

Conflict-of-interest statement: The authors declare that they have no conflicting interests.

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Manuscript source: Invited manuscript

Specialty type: Gastroenterology

Paolo Del Poggio, Sergio Lazzaroni, Unità di Epatologia, Policlinico San Marco Zingonia GSD University and Research Hospital Unità Epatologia, Osio Sotto 24040, Bergamo, Italy

Marzio Mazzoleni, Primary Care Physician, ASST Bergamo, Osio Sotto 24040, Bergamo, Italy

Andrea D'Alessio, Department of Medicine, Policlinico San Marco Zingonia, GSD University and Research Hospital, Osio Sotto 24040, Bergamo, Italy

Corresponding author: Paolo Del Poggio, MD, Consultant Physician-Scientist, Unità di Epatologia, Policlinico San Marco Zingonia GSD University and Research Hospital Unità Epatologia, Corso Europa Unità 7, Osio Sotto 24040, Bergamo, Italy.
paolo.delpoggio51@gmail.com

Abstract

Surveillance for hepatocellular carcinoma (HCC) in high-risk patients with semiannual ultrasound examinations is advocated by all international guidelines. However, as long as the identification of the population to be screened and the surveillance programs are not well implemented, the real-life impact of HCC surveillance in reducing mortality for HCC cannot be known. We propose a new approach that promotes the identification of cirrhotic patients by primary care physicians (PCPs) and referral of patients to the hepatologist for surveillance. Surveillance should be incorporated, when feasible, in a hub and spoke model of comprehensive hepatology care. Training PCPs to identify cirrhotic patients and performing surveillance in a subspecialist setting are equally important to improve the effectiveness of real-life surveillance and to decrease HCC mortality over time.

Key Words: Hepatocellular carcinoma; Cirrhosis; Ultrasound surveillance; Primary health care

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Core Tip: Ultrasound surveillance for hepatocellular carcinoma is recommended by all official guidelines for high-risk patients, but its uptake at the community level is low. We discuss the obstacles hampering its implementation and propose a hub and spoke

and hepatology

Country/Territory of origin: Italy**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
 Grade B (Very good): B, B
 Grade C (Good): 0
 Grade D (Fair): 0
 Grade E (Poor): 0

Received: March 2, 2021**Peer-review started:** March 2, 2021**First decision:** April 17, 2021**Revised:** April 24, 2021**Accepted:** August 10, 2021**Article in press:** August 10, 2021**Published online:** October 7, 2021**P-Reviewer:** Cojocariu C, Zhang L**S-Editor:** Fan JR**L-Editor:** Filipodia**P-Editor:** Wu RR

model network for the effective delivery of surveillance in the real world setting.

Citation: Del Poggio P, Mazzoleni M, Lazzaroni S, D'Alessio A. Surveillance for hepatocellular carcinoma at the community level: Easier said than done. *World J Gastroenterol* 2021; 27(37): 6180-6190

URL: <https://www.wjgnet.com/1007-9327/full/v27/i37/6180.htm>

DOI: <https://dx.doi.org/10.3748/wjg.v27.i37.6180>

INTRODUCTION

Primary liver cancer is the third leading cause of cancer related mortality worldwide [1]. It includes hepatocellular carcinoma (HCC), comprising of 75%-85% cases, intrahepatic cholangiocarcinoma (10%-15%), and other rare types [1]. The HCC death toll is the highest in East Asia and Africa, with an annual mortality rate greater than 20/100000 people [2]. Mortality is lower in Western Europe and in the United States (12-12.7/100000) but it has increased rapidly in the last decade [3]. On the other hand, Eastern Europe, Scandinavia, and India have the lowest mortality rate (less than 4/100.000). The great majority of HCC cases in the Western world are diagnosed in cirrhotic patients, while in Asia and Central Africa the most significant risk factor for HCC is chronic hepatitis B virus infection with or without cirrhosis. Therefore, patients with those risk factors (cirrhosis and/or chronic hepatitis B infection) should undergo surveillance, with the goal of identifying the tumor at an early stage when curative treatments are feasible. A randomized study of chronic hepatitis B patients in China [4], several longitudinal cohort studies in patients affected by cirrhosis of any etiology [5-7], and a meta-analysis [8] have demonstrated the benefit of ultrasound surveillance (US) in improving survival. In addition, several studies have shown that US is cost effective for the surveillance of patients affected by chronic hepatitis B and of cirrhotic patients. Indeed, HCC incidence in those populations is 0.2% and 1.5% per year respectively, which is considered acceptable to define cost effectiveness [9-11]. On the other hand, the effectiveness of US is still uncertain in young Non-Asian inactive carriers of hepatitis B surface antigen (HBsAg), in patients with chronic hepatitis C infection with advanced fibrosis, and by those with nonalcoholic fatty liver disease (NAFLD) without cirrhosis. For those reasons, the three most important international guidelines advocate periodic abdominal ultrasound scans with or without alpha-fetoprotein (AFP) in all cirrhotics and chronic hepatitis B patients, irrespective of antiviral treatment [2,12,13] as a cost effective and noninvasive surveillance modality. According to the guidelines, US should be performed on a semiannual basis, with the exclusion of decompensated cirrhotics not listed for liver transplantation, in which surveillance is considered futile.

Despite the recommendations, real-life implementation of surveillance programs is far from optimal. It has recently been shown that, in addition to an increase in the proportion of HCC diagnosed at an early stage, 64% of the cases detected in the United States between 2006 and 2012 were diagnosed at an intermediate or an advanced stage [14]. That is probably the result of the low implementation of surveillance programs, with less than 20% of cirrhotics undergoing regular surveillance [15]. Surveillance is hindered by several issues, insufficient identification of patients at risk, failure to order surveillance, failure to perform surveillance with effective tools, poor patient adherence to the surveillance program, failure to establish a care-unit network to provide effective treatment. This review aims to analyze these steps one-by-one in order to identify the obstacles hampering the implementation of surveillance in real life.

FAILURE TO IDENTIFY THE PATIENTS AT RISK

One of the most important factors responsible for the low uptake of surveillance is the failure of primary care physicians (PCPs) to identify patients at risk to be enrolled in surveillance programs. In two web-based surveys, PCPs reported lack of knowledge of current guidelines. They could not correctly identify the at-risk categories and ordered random surveillance of chronic liver disease patients [16,17]. It is noteworthy that cirrhosis is widely under diagnosed and that increased identification and surveillance

of cirrhotic patients would be very cost effective in detecting HCC at an early stage. As an example, assuming an ultrasound sensitivity of 65% for early-stage HCC[18], an increase in the detection rate of cirrhotic patients from 50% to 75% would result in a significant increase of early-stage HCC diagnosed by abdominal ultrasound. Thanks to the identification of high-risk patients, ultrasound screening would thus allow the identification of a number of early-stage HCC comparable to magnetic resonance imaging (MRI) use, which has a higher sensitivity (90%) but is more expensive and has a higher false-positive rate. Another negative consequence of the failure to identify cirrhotic patients is that the cause of liver damage is not treated, and consequently HCC would often be diagnosed in a critical patient not eligible for radical treatment anymore.

Fortunately, the performance of PCPs can be improved by training interventions[19] and by participation in specialist networks, as shown by the French experience in hepatitis C[20]. To address the problem, in 2006 we started an education program targeting 120 PCPs, aimed at the identification of cirrhotic patients and their surveillance for HCC[21]. The program was started in the southern part of the Province of Bergamo in two hospitals, Policlinico S. Marco, Zingonia, and Azienda Ospedaliera di Treviglio, that have hepatology clinics providing medium-complexity specialist care. More complex cases are referred to a tertiary care hospital in Bergamo, which has a liver transplant center. Two hepatologists had established a network of collaboration with PCPs for the management and referral of patients with liver disease, but also provided care for patients from the nearby provinces, where no specific network had been implemented. The training program consisted of a 1-year intensive course in 2006, followed by annual refreshers from 2007 to December 2013. PCPs were instructed to perform screening of all patients at risk of liver cirrhosis, *i.e.* hepatitis C virus (HCV) infection, HBsAg positivity, alcohol abuse (> 60 g/d in women and > 80 g/d in men), body mass index > 30 kg/m², and to refer them to the liver specialist for diagnostic confirmation and US planning[20]. Abdominal ultrasound was performed, and the data were analyzed, by hepatologists or by radiologists who worked at the same hospital and had strong expertise in liver cancer detection.

The results showed that 6 years after training PCPs, there was a significant increase in the number of HCC patients detected by US at an early stage and suitable for radical treatment (Figure 1). As a consequence, 3- and 5-year survival of HCC patients improved significantly from 35% to 48% and 20% to 40%, respectively ($P < 0.05$) after training. In contrast, both the proportion of HCCs detected by US, and patient survival did not change in areas where PCPs were not trained. The study has some limitations. Firstly, PCPs did not record the number of cirrhotic patients who were identified, but only the number of HCC patients who were diagnosed. Secondly, the cirrhosis criteria used by PCPs to refer the patient to the hepatologist were mainly ultrasound based using two of the following ultrasound criteria, liver surface nodularity, nonhomogeneous liver texture, left lobe or caudate lobe hypertrophy, distorted hepatic veins, spleen longitudinal diameter > 12 cm or one ultrasound criterion plus a platelet count < 130.000/mL. Currently, those criteria are obsolete, as the availability of new proprietary (*e.g.*, Fibrotest, Enhanced Liver Fibrosis, and Fibrometer) and nonproprietary biochemical scores (fibrosis-4, aspartate transaminase to platelet ratio index), and NAFLD fibrosis scores) have improved diagnostic accuracy. Nonetheless, the study showed that it is essential to establish a collaboration network among hepatologists and PCPs, and that strengthening PCP skills in identifying and referring suspected cirrhotic patients may result in an increased number of HCCs diagnosed at an early stage and improved patient survival. In the following years, the network of collaboration was extended to the whole province of Bergamo, and specific training aimed at the diagnosis of cirrhosis was incorporated into a comprehensive hepatology education program that involved 900 PCPs. The program consists of specific courses organized every 3 years by the local health authority and annual symposia organized by the tertiary care hospital of Bergamo. The percentage of HCCs diagnosed at an early stage in the following years was still high, indicating that the positive effect of training persisted in time. Indeed, 166 (77%) of 202 HCCs diagnosed in cirrhotic patients at Policlinico S. Marco Hospital from January 2014 through December 2020, were found at an early stage and could be effectively treated. It is worth noting that only 14 HCCs were diagnosed in noncirrhotic patients, seven with chronic hepatitis B and currently under surveillance, six were detected at an early stage, five had chronic hepatitis C infection, and two had noncirrhotic nonalcoholic steatohepatitis (NASH). Therefore, our real-life data confirm the adequacy of the official guidelines recommending US only in patients affected by cirrhosis or chronic hepatitis B.

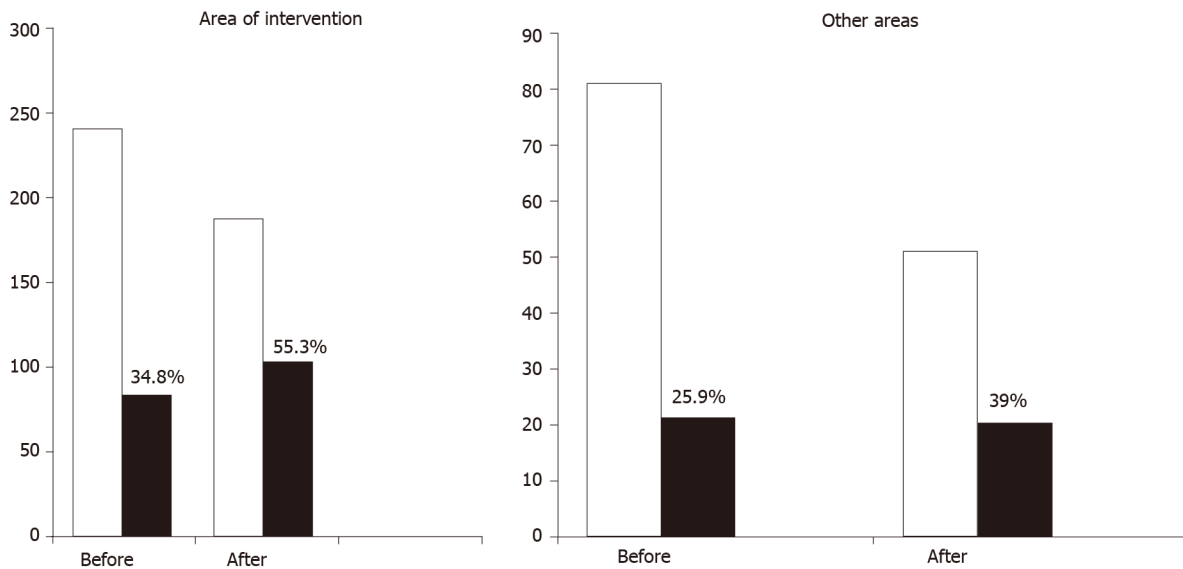


Figure 1 Hepatocellular carcinoma diagnosis before and after implementation of the training program in the area where primary care physicians were trained and in other areas where primary care physicians were not trained. White bars indicate the total number of hepatocellular carcinomas. Black bars indicate hepatocellular carcinomas diagnosed by surveillance. In the intervention area the diagnoses under surveillance increased from 85 of 244 (34.8%) to 105 of 190 (55%) after training ($\Delta = +20.5\%$, $P < 0.001$). The diagnoses increased from 21 of 81 (25.9%) to 20 of 51 (39%) in other areas ($\Delta = +13.1\%$, $P = 0.11$, not significant).

FAILURE TO ORDER SURVEILLANCE

The identification of cirrhotic patients for surveillance does not imply that surveillance will be effectively performed. In fact, surveillance is sometimes carried out by the PCP and ultrasound scans are performed by radiologists without specific expertise in liver disease. In that case, the patient is referred to the hepatologist or gastroenterologist only if a focal lesion is detected, a scenario called “population-based surveillance”. In Italy and other countries, thanks to the widespread diffusion of ultrasound equipment and the motivation of an active medical sonography society, US is directly performed by hepatologists with sonographic skills and able to perform the examinations by themselves (*i.e.* specialist or subspecialist surveillance). Population-based surveillance is mainly implemented in the United States, while specialist surveillance is more widespread in Europe and Asia. A systematic review and meta-analysis comparing the two US modalities reported a much higher effectiveness of surveillance in the specialist setting (73.7%) rather than in population-based cohorts (8.8%), with the lowest effectiveness in patients with alcoholic and NASH cirrhosis[22]. There are many reasons for the difference. PCPs and radiologists without specific expertise in liver disease may have limited knowledge of the international guidelines[17,23]. Concerns of other serious comorbidities, logistic problems such as poor accessibility of ultrasound facilities, and difficulties in the scheduling process. Consequently, the need to access low-cost, affordable ultrasound facilities may result in delays or absence of PCP surveillance[24]. Several interventions can be introduced to improve US programs, namely the use of automatic reminders for PCPs or the implementation of protocols that can be carried out by nurses or pharmacists[22]. Beste *et al*[25] reported that a primary care-oriented clinical reminder integrated into clinical records improved PCP surveillance from 18.2% to 27.6%[25], whereas no improvement was observed in the control sites (from 16.1% to 17.5%). Similarly, in a large study of 1800 cirrhotic patients, Singal *et al*[26] observed that mailed outreach invitations increased surveillance from 24% to a staggering 44.5% with no benefit seen by the addition of patient navigation [26]. Overall, it can be concluded that surveillance performed in subspecialist settings, if feasible, would be preferable to population surveillance. In the latter case, decreased use of US could be expected, and even after the interventions mentioned above (*i.e.* internal modalities such as medical reminders, nurse-based protocols, and patient navigation and outreach modalities such as mailed invitations), it was only slightly improved. Therefore, it is essential to ensure that PCPs are aware of the importance of appropriate specialist surveillance and to reinforce the need of specific education programs addressed to them.

FAILURE TO USE THE APPROPRIATE SURVEILLANCE TOOL

Liver ultrasound

Liver sonography is recommended by all existent guidelines as the standard HCC surveillance test to be used. A meta-analysis of 15 studies of cirrhotic patients showed that abdominal ultrasound had good sensitivity (84%) and excellent specificity (91%) for the detection of HCC at any stage[27]. However, the pooled sensitivity for the detection of early-stage HCC was as low as 47%, with only marginal improvement (53%) after exclusion of the studies performed before the introduction of high-density crystal probes and harmonic imaging. It is noteworthy that the sensitivity of ultrasound is characterized by a wide range of variation (from 21% to 81%), reflecting the operator dependency of US scans. In fact, in a single study performed at a university-based tertiary care center, the sensitivity of abdominal ultrasound was 82% [28]. Similarly, in a large Italian cohort study, where examinations were performed in both outside facilities and hospital wards, the sensitivity rose to 66%[18]. It is important to consider that ultrasound examinations in the United States were performed by technicians who recorded the images, which were subsequently reviewed and interpreted by radiologists. That can affect the accuracy of the examinations reported in those studies, as real-time interpretation of ultrasound findings is of paramount importance in ensuring the adequacy of the examination, especially in patients who are difficult to examine. In conclusion, it seems that pooled study results underestimate the sensitivity of ultrasound for the detection of early-stage HCC. It is more likely that the sensitivity of ultrasound carried out with high quality scanners and by well-trained doctors in a real-time manner, would be as high as 70%. Admittedly, even in optimal conditions, US fails to detect early-stage HCC in approximately one-third of the patients[18]. Two studies have addressed the causes of surveillance failure. Overall, both studies found that male sex, obesity, and advanced liver disease were associated with failure to detect HCC at an early stage[18,29]. Fatty liver, often associated with obesity and more frequently observed in males, may hinder good visualization of the liver, while advanced liver disease may produce a coarse echo pattern that masks early-stage tumors. It is important to distinguish poor visibility of the tumor by abdominal ultrasound, which represents a true limitation of this technology, from biologically aggressive tumors, which may show an infiltrative or rapidly growing pattern that may be difficult to detect regardless of the diagnostic tool.

Computed tomography and magnetic resonance imaging

The use of CT or MRI can obviate the above-mentioned technical limitations of ultrasound, but they rarely can identify an aggressive tumor at an early stage. In one study, 20% of the ultrasound examinations were considered technically inadequate for excluding HCC[29]. In another study, 32% of HCCs were detected beyond the early stage by semiannual US, 12% of them showing biologically aggressive features, *i.e.*, AFP > 1000 ng/mL, vascular thrombosis, distant metastasis, or infiltrative pattern[18]. Therefore, technical limitations of US to detect early-stage HCC can be deemed to be around 20%, hence it is important that ultrasound reports include a statement about the quality of the examination and the potential recommendation to perform second-level imaging (CT or MRI). MRI has a sensitivity of 83.7% for the detection of early-stage HCC[30] and should be preferred to CT, which has lower sensitivity (62.5%), similar to that of ultrasound[31]. However, it is noticeable that biologically aggressive tumors are poorly detected by MRI (16% failure to detect HCC) as well as by US (12% failure). Those tumors thus represent a hardcore of HCCs eluding both kinds of imaging surveillance. The good news is that only a small percentage of HCCs have those characteristics. However, it should be recognized that the pattern of HCC growth is heterogeneous[32] and many indolent tumors can develop an aggressive pattern with time, as shown by an increase of the percentage of biologically aggressive tumors detected by annual compared with semiannual surveillance, (*i.e.* 28% *vs* 12%) [18]. The possibility that indolent HCCs might transform into more aggressive tumors with time has raised some concerns of the common real-life practice of performing annual instead of semiannual MRI to reduce surveillance cost

Contrast-enhanced ultrasound

Contrast-enhanced US with intravascular agents (*e.g.*, Levovist, Sonovue) has a limited role in surveillance as it is impossible to scan the whole liver in the arterial phase when small tumors are detected[33]. On the other hand, perfluorocarbon (Sonazoid) seems to a promising agent[34], as it is taken up and retained by Kupffer cells for 60 min after

bolus injection, allowing a scan of the entire liver in the late phase when HCC appears as a black hole. Sonazoid-enhanced US might therefore be useful to detect HCC developing in livers with a coarse echotexture, but it cannot be of any advantage in obese patients or severe fatty livers, where CT or MRI remain the only option to accurately exclude HCC.

AFP

The sensitivity of AFP to detect early-stage HCC is too low to be used alone as a surveillance tool[35]. Only the Asian-Pacific Guidelines recommend the use of AFP in surveillance programs, with a cutoff of 200 ng/mL[2]. This cutoff is highly specific but reduces AFP sensitivity to a level as low as 22%[12]. However, new and effective pharmacological treatment of hepatitis B and C may remove false-positive AFP results caused by necro-inflammatory activity and enable the use of lower cutoff levels, providing better AFP sensitivity without compromising its specificity. Another method to improve AFP diagnostic accuracy is to monitor its changes over time[36]. An algorithm including AFP variations has been created and was tested in the Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis Trial cohort, with good results in identifying patients at increased risk of HCC[37]. A recent meta-analysis showed that the addition of AFP levels to abdominal ultrasound improved the overall sensitivity for the detection of early-stage HCC from 45% to 63%[27], but as pointed out before, the low sensitivity of US in the meta-analysis raises doubts on the quality of the ultrasound examinations. It therefore remains an open question whether AFP can improve the performance of properly executed sonography. It is important to stress that the addition of AFP screening to abdominal sonography could adversely affect the already low level of surveillance application by PCPs because of the logistic and financial burden introduced by duplicating the surveillance tool. In our real-life practice we assess AFP levels alongside abdominal US only in patients with cured hepatitis C or well-controlled chronic hepatitis B and optimal adherence to follow-up visits. A change in AFP values over time prompts performing second-level imaging, particularly in cases with a coarse echo pattern on sonography. On the other hand, stable AFP levels permit advising the continuation of standard US, avoiding additional cost.

New biochemical markers

In recent years, new markers have been proposed for the diagnosis of early HCC. Each of them by itself does not seem to confer any benefit in diagnostic accuracy compared with US with or without AFP[35]. However, a combination of AFP-L3, AFP, and des-gamma-carboxy prothrombin was tested in a large study and proved to have a sensitivity greater than 60% for early HCC, which is similar to the sensitivity of currently approved surveillance tools[38]. The algorithm is interesting, and if confirmed could be used as an alternative to ultrasound in the setting of population surveillance, especially where ultrasound scanners are not available or not accessible.

THE PROBLEM OF ADHERENCE

Patient adherence is key to the effectiveness of the surveillance program. Racial and ethnic minorities have poor awareness of surveillance programs, probably because of their low socioeconomic status. Patients also report difficulties scheduling surveillance ultrasound, concerns of the cost, need of off-work days, and difficulties reaching the facilities where the exam is performed[39]. The difficulties have a greater impact on subspecialty-based than on population-based surveillance, and should be addressed by appropriate interventions. In our hospital, the great majority of examinations are performed by hepatologists (PD and SL) and each appointment is directly booked by the specialist, thus making the scheduling process much easier. Visits and US examinations are reimbursed by the National Health Care System, with no additional cost for the patient. They are both performed at the same time to minimize off-work time, and if the patient is under antiviral treatment, the drug can be collected from the hospital pharmacy on the same day. Table 1 shows adherence to surveillance in 362 cirrhotic patients followed from January 2013 through December 2020 in our outpatient clinic. Adherence was defined as the performance of regular annual or semiannual ultrasound examinations in the last 24 months. Overall adherence to surveillance was rather good and only slightly lower than that observed in studies from other subspecialty clinics, (*i.e.* 65% *vs* 73%)[22]. It should be highlighted that in 2020 Northern Italy was heavily hit by the coronavirus disease 2019 pandemic and that the liver clinic was

Table 1 Adherence to surveillance by 362 cirrhotic patients followed from January 2013 through December 2020 at the hepatology unit of Policlinico S. Marco

Etiology of cirrhosis	Adherent	Semiannual	Annual	Nonadherent
Alcoholic (103)	55 (52%)	31 (56%)	24 (44%)	48 (46%)
HBV (53)	39 (73%)	35 (90%)	4 (10%)	14 (27%)
HCV (164)	119 (72%)	101 (85%)	18 (15%)	45 (28%)
NAFLD (42)	24 (57%)	17 (71%)	7 (29%)	18 (43%)
Total: 362	237 (65%)	184 (77%)	53 (23%)	125 (35%)

Adherence was defined as the performance of regular annual or semiannual ultrasound examinations in the previous 24 mo. HBV: Hepatitis B virus; HCV: Hepatitis C virus; NAFLD: Nonalcoholic fatty liver disease.

closed down for 2 months until April 2020. The restrictions and the fear of being infected and contracting the disease might have induced patients to avoid medical appointments, as observed for other screening programs during the pandemic. Despite that, nearly two-thirds of the patients continued surveillance, which in 77% of the cases was semiannual and in line with the official recommendations. It should be emphasized that the definition of adherence is not unequivocal, as some investigators used restrictive definitions while others, as we did, use operational definitions. Patients who underwent at least 1 or 2 surveillance exams in the last 12 months were considered adherent to the surveillance program. Moreover, as adherence decreases over time, studies with longer follow-up show lower adherence rates and cannot be compared with studies that have a shorter follow-up. To solve this conundrum it has been proposed to define adherence to the surveillance program as the proportion of time up-to-date with screening[22], although in retrospective studies complete patient data are often lacking, and this parameter may be difficult to achieve. In accord with other studies, we found a lower adherence to surveillance programs in alcoholic and metabolic cirrhotic patients (NAFLD). In those patients, the time interval between screening exams was more frequently annual than semiannual. On the other hand, patients affected by cirrhosis secondary to hepatitis B and C, had a higher adherence to the surveillance programs (72% and 73% respectively) and exams were almost exclusively performed with semiannual periodicity. The reasons for the low adherence in the former categories are multifactorial. Lack of family support and low socioeconomic status are important and can hinder the access to the health care system as well as social stigma associated with alcohol abuse and obesity. It is well known that marginalized and stigmatized patients are more dependent on a good relationship with the healthcare provider than on getting the right information from scientific sources or mail reminders. They may also overestimate the prescription of drugs compared with regular screening tests, and perceive the periodicity of ultrasound examinations as a mere waste of time. It is therefore important to establish an empathic nonjudgmental relationship with those patients. The ultrasound examination should be integrated with the hepatologist consultation, a longer time for the visit should be scheduled, medical issues should be discussed, and drugs prescribed if necessary. It is important to make the patient understand that surveillance is essential to take care of their liver disease. For that purpose, it would be helpful to establish a close collaboration with Alcoholics Anonymous or other self-help groups, that could help the patients to be actively involved and aware of the importance of surveillance.

CONCLUSION

In conclusion, despite generalized consensus of all scientific guidelines on the utility of surveillance for HCC in high-risk patients, the implementation of surveillance at the community level is far from ideal. Low access to surveillance programs is associated with a lower number of HCC diagnosed at an early stage and decreased survival. Therefore, it is important to study the obstacles hampering the adherence to surveillance of the high-risk population in order to implement appropriate interventions.

Adherence to surveillance programs is higher in hospital/subspecialty-based surveillance compared with population-based surveillance, in which tests are ordered by PCPs and performed by general radiologists. Subspecialty-based surveillance should therefore be the first choice when feasible. However, the geographic location of the facilities and the distance from the hospital may result in population surveillance as the only available choice. In both cases, lack of identification of the at-risk categories by PCPs, (*i.e.* cirrhotic patients and chronic hepatitis B patients), is the most important issue hindering implementation of adequate surveillance. Education programs targeted to PCPs to improve their skills in identifying the patients at risk can facilitate prompt referral to the hepatologist/gastroenterologist for US. PCPs should be encouraged to use biochemical scores to raise the suspicion of cirrhosis, and if feasible, portable elastography scanners. Once the diagnosis of cirrhosis has been established by transient elastography, acoustic radiation force impulse elastography, or other modalities, the patient should be followed up in a specialty setting. Regarding the surveillance tools, real-life experience confirms that semiannual ultrasound examination with the addition of sequential AFP monitoring in selected cases is the most appropriate method, with a sensitivity of about 70%. Ultrasound examinations should be of high quality and hence preferably performed by radiologists with good expertise in liver imaging, or when feasible, by the hepatologist himself. When ultrasound examinations are unsatisfactory (about 20% of cases), it should be explicitly noted in the sonographic report and the patient preferably surveilled with an annual MRI, which brings the total detection rate of early-stage HCC up to 85%. Fifteen percent of HCCs are aggressive tumors that cannot be diagnosed at an early stage with the currently available tools. Adherence to scheduled examinations is still a problem, particularly in some categories of patients, *i.e.* alcoholic and NAFLD cirrhotic patients. In order to improve patient adherence, a less complex approach that reducing the number of visits to the hospital and reducing bureaucratic procedures should be used. Once a diagnosis of HCC is made. It should be promptly treated in the appropriate setting, with evaluation of the necessity to refer the patient to a tertiary care hospital for more advanced treatments or to be evaluated for liver transplantation. **Figure 2** shows the hub and spoke model of care of cirrhotic patients implemented in our province. According to the model, cirrhotic patients are identified by PCPs using appropriate screening tests. The patients are then referred to the liver clinics of general hospitals (Spokes) for diagnosis confirmation and implementation of surveillance programs. Therapeutic interventions are performed locally when feasible or the patient is referred to the tertiary referral hospital (Hub) for further treatment.

KEY TAKE AWAY MESSAGES

Surveillance for HCC in cirrhotic patients and chronic hepatitis B patients allows detection of the tumor at an early stage and improves survival.

International guidelines recommend semiannual ultrasound with or without AFP monitoring in these patients, but surveillance implementation at the community level is low.

Education programs targeting PCP and aiming at improving the identification and referral of patients at risk of HCC should be implemented.

Subspecialty-based surveillance performed by the hepatologist or gastroenterologist in the setting of the liver clinic of a general hospital is the preferred model, when feasible.

Ultrasound and MRI should be used sequentially in case of inadequate sonography.

Surveillance should be incorporated into the specific care and follow-up provided by the liver clinic to enhance adherence.

The liver clinic of the general hospital should be integrated into a hub and spoke model of care alongside PCPs and tertiary referral hospitals to ensure proper access to care.

ACKNOWLEDGMENTS

We thank Dr. Francesca De Martini for scientific and language revision of the English text.

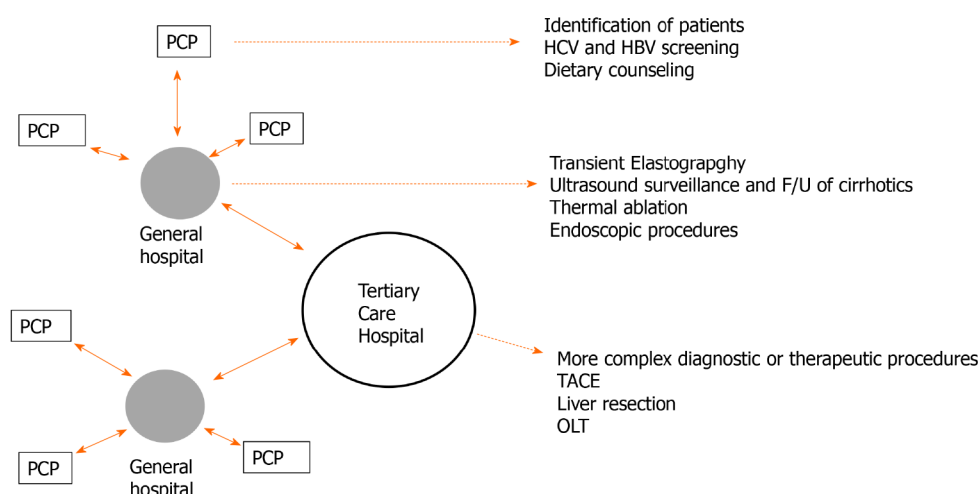


Figure 2 Hub and spoke model for the diagnosis and follow-up of cirrhotic patients by primary care physicians in the province of Bergamo. In the model, ultrasound surveillance and follow-up of cirrhotics are performed by hepatologists in general hospitals. HBV: Hepatitis B virus; HCV: Hepatitis C virus; OLT: Orthotopic liver transplantation; PCP: Primary care physicians.

REFERENCES

- Sung H**, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021; **71**: 209-249 [PMID: [33538338](#) DOI: [10.3322/caac.21660](#)]
- Omata M**, Cheng AL, Kokudo N, Kudo M, Lee JM, Jia J, Tateishi R, Han KH, Chawla YK, Shiina S, Jafri W, Payawal DA, Ohki T, Ogasawara S, Chen PJ, Lesmana CRA, Lesmana LA, Gani RA, Obi S, Dokmeci AK, Sarin SK. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. *Hepatol Int* 2017; **11**: 317-370 [PMID: [28620797](#) DOI: [10.1007/s12072-017-9799-9](#)]
- Tapper EB**, Parikh ND. Mortality due to cirrhosis and liver cancer in the United States, 1999-2016: observational study. *BMJ* 2018; **362**: k2817 [PMID: [30021785](#) DOI: [10.1136/bmj.k2817](#)]
- Zhang BH**, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. *J Cancer Res Clin Oncol* 2004; **130**: 417-422 [PMID: [15042359](#) DOI: [10.1007/s00432-004-0552-0](#)]
- El-Serag HB**, Kramer JR, Chen GJ, Duan Z, Richardson PA, Davila JA. Effectiveness of AFP and ultrasound tests on hepatocellular carcinoma mortality in HCV-infected patients in the USA. *Gut* 2011; **60**: 992-997 [PMID: [21257990](#) DOI: [10.1136/gut.2010.230508](#)]
- Pateron D**, Ganne N, Trinchet JC, Auroousseau MH, Mal F, Meicler C, Coderc E, Reboullet P, Beaugrand M. Prospective study of screening for hepatocellular carcinoma in Caucasian patients with cirrhosis. *J Hepatol* 1994; **20**: 65-71 [PMID: [7515408](#) DOI: [10.1016/s0168-8278\(05\)80468-4](#)]
- Trevisani F**, De Notariis S, Rapaccini G, Farinati F, Benvegnù L, Zoli M, Grazi GL, Del PP, Di N, Bernardi M; Italian Liver Cancer Group. Semiannual and annual surveillance of cirrhotic patients for hepatocellular carcinoma: effects on cancer stage and patient survival (Italian experience). *Am J Gastroenterol* 2002; **97**: 734-744 [PMID: [11922571](#) DOI: [10.1111/j.1572-0241.2002.05557.x](#)]
- Singal AG**, Pillai A, Tiro J. Early detection, curative treatment, and survival rates for hepatocellular carcinoma surveillance in patients with cirrhosis: a meta-analysis. *PLoS Med* 2014; **11**: e1001624 [PMID: [24691105](#) DOI: [10.1371/journal.pmed.1001624](#)]
- Sarasin FP**, Giostra E, Hadengue A. Cost-effectiveness of screening for detection of small hepatocellular carcinoma in western patients with Child-Pugh class A cirrhosis. *Am J Med* 1996; **101**: 422-434 [PMID: [8873514](#) DOI: [10.1016/S0002-9343\(96\)00197-0](#)]
- Lin OS**, Keeffe EB, Sanders GD, Owens DK. Cost-effectiveness of screening for hepatocellular carcinoma in patients with cirrhosis due to chronic hepatitis C. *Aliment Pharmacol Ther* 2004; **19**: 1159-1172 [PMID: [15153169](#) DOI: [10.1111/j.1365-2036.2004.01963.x](#)]
- Thompson Coon J**, Rogers G, Hewson P, Wright D, Anderson R, Cramp M, Jackson S, Ryder S, Price A, Stein K. Surveillance of cirrhosis for hepatocellular carcinoma: systematic review and economic analysis. *Health Technol Assess* 2007; **11**: 1-206 [PMID: [17767898](#) DOI: [10.3310/hta11340](#)]
- European Association for the Study of the Liver**. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. *J Hepatol* 2018; **69**: 182-236 [PMID: [29628281](#) DOI: [10.1016/j.jhep.2018.03.019](#)]
- Heimbach JK**, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, Zhu AX, Murad MH, Marrero JA. AASLD guidelines for the treatment of hepatocellular carcinoma. *Hepatology* 2018; **67**: 358-380 [PMID: [28130846](#) DOI: [10.1002/hep.29086](#)]
- Noone A**, Howlader N, Krapcho M. Cancer statistics review, 1975-2015. Bethesda, MD: National

- Cancer Institute, 2018
- 15 **Singal AG**, Yopp A, S Skinner C, Packer M, Lee WM, Tiro JA. Utilization of hepatocellular carcinoma surveillance among American patients: a systematic review. *J Gen Intern Med* 2012; **27**: 861-867 [PMID: [22215266](#) DOI: [10.1007/s11606-011-1952-x](#)]
 - 16 **Simmons OL**, Feng Y, Parikh ND, Singal AG. Primary Care Provider Practice Patterns and Barriers to Hepatocellular Carcinoma Surveillance. *Clin Gastroenterol Hepatol* 2019; **17**: 766-773 [PMID: [30056183](#) DOI: [10.1016/j.cgh.2018.07.029](#)]
 - 17 **Dalton-Fitzgerald E**, Tiro J, Kandunoori P, Halm EA, Yopp A, Singal AG. Practice patterns and attitudes of primary care providers and barriers to surveillance of hepatocellular carcinoma in patients with cirrhosis. *Clin Gastroenterol Hepatol* 2015; **13**: 791-8.e1 [PMID: [25019694](#) DOI: [10.1016/j.cgh.2014.06.031](#)]
 - 18 **Del Poggio P**, Olmi S, Ciccarese F, Di Marco M, Rapaccini GL, Benvegnù L, Borzio F, Farinati F, Zoli M, Giannini EG, Caturelli E, Chiaramonte M, Trevisani F; Italian Liver Cancer (ITA. LI.CA) Group. Factors that affect efficacy of ultrasound surveillance for early stage hepatocellular carcinoma in patients with cirrhosis. *Clin Gastroenterol Hepatol* 2014; **12**: 1927-33.e2 [PMID: [24582947](#) DOI: [10.1016/j.cgh.2014.02.025](#)]
 - 19 **Cozzolongo R**, Cuppone R, Petruzzi J, Stroffolini T, Manghisi OG. Approach of primary care physicians to hepatitis C: an educational survey from a Southern Italian area. *J Infect* 2005; **51**: 396-400 [PMID: [16321651](#) DOI: [10.1016/j.jinf.2004.12.004](#)]
 - 20 **Delarocque-Astagneau E**, Meffre C, Dubois F, Pioche C, Le Strat Y, Roudot-Thoraval F, Hillon P, Silvain C, Dhumeaux D, Desenclos JC; Hepatitis C Surveillance System Committee; Scientific Committee for the National Prevalence Survey of Hepatitis B and C Markers. The impact of the prevention programme of hepatitis C over more than a decade: the French experience. *J Viral Hepat* 2010; **17**: 435-443 [PMID: [19780936](#) DOI: [10.1111/j.1365-2893.2009.01196.x](#)]
 - 21 **Del Poggio P**, Olmi S, Ciccarese F, Mazzoleni M, Jazzetti M, Jomoletti C, Mattiello M, Del Poggio A, Portugali V, Stroffolini T. A training program for primary care physicians improves the effectiveness of ultrasound surveillance of hepatocellular carcinoma. *Eur J Gastroenterol Hepatol* 2015; **27**: 1103-1108 [PMID: [26049705](#) DOI: [10.1097/MEG.0000000000000404](#)]
 - 22 **Wolf E**, Rich NE, Marrero JA, Parikh ND, Singal AG. Use of Hepatocellular Carcinoma Surveillance in Patients With Cirrhosis: A Systematic Review and Meta-Analysis. *Hepatology* 2021; **73**: 713-725 [PMID: [32383272](#) DOI: [10.1002/hep.31309](#)]
 - 23 **McGowan CE**, Edwards TP, Luong MU, Hayashi PH. Suboptimal surveillance for and knowledge of hepatocellular carcinoma among primary care providers. *Clin Gastroenterol Hepatol* 2015; **13**: 799-804 [PMID: [25117773](#) DOI: [10.1016/j.cgh.2014.07.056](#)]
 - 24 **Farvardin S**, Patel J, Khambaty M, Yerokun OA, Mok H, Tiro JA, Yopp AC, Parikh ND, Marrero JA, Singal AG. Patient-reported barriers are associated with lower hepatocellular carcinoma surveillance rates in patients with cirrhosis. *Hepatology* 2017; **65**: 875-884 [PMID: [27531684](#) DOI: [10.1002/hep.28770](#)]
 - 25 **Beste LA**, Ioannou GN, Yang Y, Chang MF, Ross D, Dominitz JA. Improved surveillance for hepatocellular carcinoma with a primary care-oriented clinical reminder. *Clin Gastroenterol Hepatol* 2015; **13**: 172-179 [PMID: [24813175](#) DOI: [10.1016/j.cgh.2014.04.033](#)]
 - 26 **Singal AG**, Tiro JA, Murphy CC, Marrero JA, McCallister K, Fullington H, Mejias C, Waljee AK, Pechero Bishop W, Santini NO, Halm EA. Mailed Outreach Invitations Significantly Improve HCC Surveillance Rates in Patients With Cirrhosis: A Randomized Clinical Trial. *Hepatology* 2019; **69**: 121-130 [PMID: [30070379](#) DOI: [10.1002/hep.30129](#)]
 - 27 **Tzartzeva K**, Obi J, Rich NE, Parikh ND, Marrero JA, Yopp A, Waljee AK, Singal AG. Surveillance Imaging and Alpha Fetoprotein for Early Detection of Hepatocellular Carcinoma in Patients With Cirrhosis: A Meta-analysis. *Gastroenterology* 2018; **154**: 1706-1718.e1 [PMID: [29425931](#) DOI: [10.1053/j.gastro.2018.01.064](#)]
 - 28 **Bolondi L**, Sofia S, Siringo S, Gaiani S, Casali A, Zironi G, Piscaglia F, Gramantieri L, Zanetti M, Sherman M. Surveillance programme of cirrhotic patients for early diagnosis and treatment of hepatocellular carcinoma: a cost effectiveness analysis. *Gut* 2001; **48**: 251-259 [PMID: [11156649](#) DOI: [10.1136/gut.48.2.251](#)]
 - 29 **Simmons O**, Fetzter DT, Yokoo T, Marrero JA, Yopp A, Kono Y, Parikh ND, Browning T, Singal AG. Predictors of adequate ultrasound quality for hepatocellular carcinoma surveillance in patients with cirrhosis. *Aliment Pharmacol Ther* 2017; **45**: 169-177 [PMID: [27862091](#) DOI: [10.1111/apt.13841](#)]
 - 30 **Kim SY**, An J, Lim YS, Han S, Lee JY, Byun JH, Won HJ, Lee SJ, Lee HC, Lee YS. MRI With Liver-Specific Contrast for Surveillance of Patients With Cirrhosis at High Risk of Hepatocellular Carcinoma. *JAMA Oncol* 2017; **3**: 456-463 [PMID: [27657493](#) DOI: [10.1001/jamaoncol.2016.3147](#)]
 - 31 **Pocha C**, Dieperink E, McMaken KA, Knott A, Thuras P, Ho SB. Surveillance for hepatocellular cancer with ultrasonography vs. computed tomography -- a randomised study. *Aliment Pharmacol Ther* 2013; **38**: 303-312 [PMID: [23750991](#) DOI: [10.1111/apt.12370](#)]
 - 32 **Rich NE**, John BV, Parikh ND, Rowe I, Mehta N, Khatri G, Thomas SM, Anis M, Mendiratta-Lala M, Hernandez C, Odewole M, Sundaram LT, Konjeti VR, Shetty S, Shah T, Zhu H, Yopp AC, Hoshida Y, Yao FY, Marrero JA, Singal AG. Hepatocellular Carcinoma Demonstrates Heterogeneous Growth Patterns in a Multicenter Cohort of Patients With Cirrhosis. *Hepatology* 2020; **72**: 1654-1665 [PMID: [32017165](#) DOI: [10.1002/hep.31159](#)]
 - 33 **Lencioni R**, Piscaglia F, Bolondi L. Contrast-enhanced ultrasound in the diagnosis of hepatocellular

- carcinoma. *J Hepatol* 2008; **48**: 848-857 [PMID: 18328590 DOI: 10.1016/j.jhep.2008.02.005]
- 34 **Kudo M**, Hatanaka K, Kumada T, Toyoda H, Tada T. Double-contrast ultrasound: a novel surveillance tool for hepatocellular carcinoma. *Am J Gastroenterol* 2011; **106**: 368-370 [PMID: 21301463 DOI: 10.1038/ajg.2010.432]
- 35 **Kanwal F**, Singal AG. Surveillance for Hepatocellular Carcinoma: Current Best Practice and Future Direction. *Gastroenterology* 2019; **157**: 54-64 [PMID: 30986389 DOI: 10.1053/j.gastro.2019.02.049]
- 36 **Lee E**, Edward S, Singal AG, Lavieri MS, Volk M. Improving screening for hepatocellular carcinoma by incorporating data on levels of α -fetoprotein, over time. *Clin Gastroenterol Hepatol* 2013; **11**: 437-440 [PMID: 23247324 DOI: 10.1016/j.cgh.2012.11.029]
- 37 **Tayob N**, Lok AS, Do KA, Feng Z. Improved Detection of Hepatocellular Carcinoma by Using a Longitudinal Alpha-Fetoprotein Screening Algorithm. *Clin Gastroenterol Hepatol* 2016; **14**: 469-475.e2 [PMID: 26260109 DOI: 10.1016/j.cgh.2015.07.049]
- 38 **Berhane S**, Toyoda H, Tada T, Kumada T, Kagebayashi C, Satomura S, Schweitzer N, Vogel A, Manns MP, Benckert J, Berg T, Ebker M, Best J, Dechêne A, Gerken G, Schlaak JF, Weinmann A, Wörns MA, Galle P, Yeo W, Mo F, Chan SL, Reeves H, Cox T, Johnson P. Role of the GALAD and BALAD-2 Serologic Models in Diagnosis of Hepatocellular Carcinoma and Prediction of Survival in Patients. *Clin Gastroenterol Hepatol* 2016; **14**: 875-886.e6 [PMID: 26775025 DOI: 10.1016/j.cgh.2015.12.042]
- 39 **Wong RJ**, Ahmed A; Hepatocellular Carcinoma Research Committee of the Chronic Liver Disease Foundation. Understanding Gaps in the Hepatocellular Carcinoma Cascade of Care: Opportunities to Improve Hepatocellular Carcinoma Outcomes. *J Clin Gastroenterol* 2020; **54**: 850-856 [PMID: 33030855 DOI: 10.1097/MCG.0000000000001422]



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