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Editorial

Hepatocellular carcinoma surveillance in non-alcoholic fatty liver disease – who and how?

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Non-alcoholic fatty liver disease (NAFLD) is the fastest-growing cause of hepatocellular carcinoma (HCC) globally.[1] The burden of NAFLD-related HCC is predicted to increase further, in tandem with the obesity epidemic.[2] NAFLD encompasses a spectrum of histological severity, ranging from non-alcoholic fatty liver to non-alcoholic steatohepatitis (NASH), which can consequently progress to liver fibrosis and cirrhosis.[3] One of the strongest risk factors for NAFLD-HCC is fibrosis stage,[4,5] and a prospective multi-centre study found that incidence of HCC per 100 person-years increased with fibrosis stage.[6]

Surveillance is associated with early detection of HCC and a higher likelihood of receiving curative treatment.[7] Patients with early HCC are more likely to be eligible for curative treatment such as ablation, surgical resection, or liver transplantation, with 5-year survival rates of >70%.[8,9] As such, surveillance is linked with improved overall survival.[7] Despite the rise in the incidence of NAFLD-HCC,[10] key questions remain regarding HCC surveillance in NAFLD patients–namely who to survey, and how to survey these patients.

In a recent issue of *Clinical and Molecular Hepatology*, El Dahan et al.[11] highlight that HCC surveillance should be limited to NAFLD patients with cirrhosis, and there is currently no consensus regarding HCC surveillance in NAFLD patients without cirrhosis. Currently, the American Gastroenterology Association (AGA) and the European Association for the Study of the Liver (EASL) suggest that HCC surveillance may be considered selected non-cirrhotic NAFLD patients.[12,13] The AGA clinical practice update recommends the consideration of HCC surveillance in patients with advanced ≥F3 fibrosis, and proposes specific cut-offs on non-invasive tests (NITs) for consideration of surveillance–specifically, liver stiffness measurement of 16.1 kPa on vibration-controlled transient elastography (VCTE) and 5 kPa on magnetic resonance elastography (MRE) are cut-off values at which patients should consider HCC surveillance.[12] EASL guidelines recommend that HCC surveillance may be considered in patients with advanced fibrosis diagnosed either on biopsy or elastography and acknowledge that surveillance in non-cirrhotic NAFLD

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patients remains unclear.[13]

To improve HCC surveillance in NAFLD, further efforts are needed to improve assessment of fibrosis stage, and identify NAFLD patients with advanced fibrosis at elevated risk of HCC. At present, AGA and EASL advocate a sequential approach using NITs (fibrosis-index 4 [FIB-4] followed by VCTE) to identify NAFLD patients with advanced fibrosis.[14] A prospective study involving 5 tertiary European centres showed that this strategy was able to predict risk of liver-related events, which included both complications of cirrhosis and HCC.[15] Longitudinal assessment of NITs has also been proposed as a method of monitoring changes in fibrosis over time and could facilitate early detection of progression to advanced fibrosis or cirrhosis.[16,17] Additionally, there are emerging data that NITs have potential for HCC risk stratification in NAFLD patients. Several studies in Asia and Europe have found that elevated FIB-4 was associated with a substantially increased risk of HCC over a median follow-up of 7–10 years.[18-20] More research is required to evaluate whether i) other NITs such as VCTE and MRE and ii) longitudinal information on NITs are correlated with HCC risk.

Next, HCC surveillance should be individualised in NAFLD patients without cirrhosis. Restricting HCC surveillance in NAFLD to patients with cirrhosis could miss a significant proportion of NAFLD patients who develop HCC. Compared to HCC of other etiologies, a higher percentage of NAFLD-HCC patients were non-cirrhotic (38.5% vs. 14.6%).[10] This may have contributed to lower HCC surveillance rates among NAFLD-HCC patients, as nearly 40% of NAFLD-HCC patients would not have had an indication for routine surveillance based on current guidelines. However, extending existing society recommendations to all non-cirrhotic NAFLD patients has major implications. The incidence of HCC in patients with non-cirrhotic NAFLD is low at approximately 0.1–1.3 per 1,000 person-years.[2] HCC surveillance in this large and rising population of NAFLD patients is neither feasible nor cost-effective.

There is a wide heterogeneity of HCC risk in non-cirrhotic NAFLD patients–apart from degree of fibrosis, other factors such as genetic polymorphisms, age, gender, obesity, and type 2 diabetes have been associated with HCC risk.[4] It would be more accurate to assess HCC risk directly, rather than extrapolating HCC risk from fibrosis stage. Several genome-wide association studies have identified single nucleotide polymorphisms (SNPs) such as patatin-like phospholipase domain-containing protein 3 (*PNPLA3*) which could be linked to increased risk of HCC.[21] Polygenic risk scores including these SNPs have been found to improve detection of HCC particularly in individuals with dysmetabolism, and was able to predict HCC independently of presence of severe fibrosis in NAFLD patients.[22] It has been suggested that risk factors and estimates of fibrosis stage could also be combined into risk calculators or risk prediction models to identify NAFLD patients at higher risk of HCC who would benefit from surveillance.[4,11] A HCC risk calculator comprising 7 parameters derived from clinical characteristics and serum lab tests has previously been developed in patients with NAFLD cirrhosis to estimate HCC risk,[23] although this has not been externally validated. Another novel risk prediction model comprising age, platelet count, serum aspartate aminotransferase, and liver stiffness based on VCTE has demonstrated utility in prediction of HCC risk in NAFLD patients.[24]

El Dahan et al.[11] comment that the current method most often utilized for HCC surveillance, ultrasound (US) +/- alphafetoprotein (AFP), is inadequate for early detection of HCC. US has a relatively poor sensitivity of <50% for early detection of HCC.[25] Furthermore, patients with NASH cirrhosis were found to be more likely to have limited visualisation on ultrasound.[26,27] Surveillance failure could be attributed to the presence of subcutaneous fat, focal fatty infiltration, and heterogeneity of liver parenchyma, which hinder the identification of smaller lesions.[28] The AGA clinical practice update advises that the adequacy of ultrasound for HCC surveillance should be documented, and if inadequate, other imaging modalities such as computed tomography (CT) scan or magnetic resonance imaging (MRI) should be considered.[12] As mentioned by El Dahan et al.[11], numerous alternative imaging techniques such as abbreviated MRI protocols have been proposed, but at present, data on their utility and cost-effec-

Abbreviations:

NAFLD, non-alcoholic fatty liver disease; HCC, hepatocellular carcinoma; NASH, non-alcoholic steatohepatitis; AGA, American Gastroenterology Association; EASL, European Association for the Study of the Liver; NITs, non-invasive tests; VCTE, vibration-controlled transient elastography; MRE, magnetic resonance elastography; FIB-4, fibrosis-index 4; SNPs, single nucleotide polymorphisms; US, ultrasound; AFP, alphafetoprotein; CT, computed tomography; MRI, magnetic resonance imaging; AASLD, American Association for the Study of Liver Disease

tiveness is lacking.

Both AGA and American Association for the Study of Liver Disease (AASLD) support US +/- AFP, whereas EASL supports US alone for HCC surveillance.[12,13,29] A meta-analysis found that pooled sensitivity for detection of early HCC improved from 45% with US alone to 63% with addition of AFP to US.[25] EASL also mentions that combining AFP and US leads to a modest 6–8% increase in detection of HCC.[13] Given the inadequate visualisation on US in NAFLD patients, the addition of AFP to US should be considered to maximise the possibility of detection of HCC. El Dahan et al.[11] discuss alternative biomarker-based surveillance tools such as GALAD and other novel biomarkers. Recent evidence suggests that liquid biopsy techniques such as methylation profiling of circulating tumour DNA have the potential to improve detection rates and transform the future of surveillance.[30]

In conclusion, a multi-pronged strategy is required to optimise HCC surveillance in NAFLD patients. Improved risk stratification of NAFLD patients who might warrant HCC surveillance, as well as the adoption of more accurate biomarker- or imaging-based surveillance modalities may help address the challenges of HCC surveillance in NAFLD.

Authors' contribution

Conceptualisation and Design: Margaret LP Teng, Daniel Q. Huang. Acquisition of Data, Analysis and Interpretation of Data: All authors Writing – original draft: Margaret LP Teng, Daniel Q. Huang. Writing – revision and final approval of version to be published: All authors.

Conflicts of Interest

The authors have no conflicts to disclose.

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