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Editorial

Hepatocellular carcinoma screening in NAFLD: The paradox of nearly half the cases arising in non-cirrhotic low risk patients

Liver cancer is in the top three leading causes of death from cancer worldwide. Hepatocellular carcinoma (HCC) accounts for 85% of primary liver cancers and develops in patients with chronic liver disease (CLD). The progressive increase in the prevalence of nonalcoholic fatty liver disease (NAFLD), which recently reached up to 30% of the global population [1], and the recent effective treatment for hepatitis C, results in NAFLD being the most rapidly increasing etiology for HCC. Since the beginning of the millennium, the proportion of NAFLD-attributable HCC increased up to 8-fold, currently accounting for 15% of HCC cases [2].

NAFLD-associated HCC has the particularity of being 5 times more frequent in the pre-cirrhotic phase of the disease, as compared with other etiologies of CLD [3]. Actually, 2 out of 5 patients with NAFLD-associated HCC do not have cirrhosis [3]. Importantly, the absence of cirrhosis does not seem to independently impact survival, which rather is dependent on the cancer stage and treatment provided.

From another perspective, considering the risk of NAFLD patients developing HCC, those without cirrhosis have 100 times lower risk: the HCC annual incidence rate is around 3.8% in patients with cirrhosis (similar to other etiologies) and 0.03% in patients in the pre-cirrhotic state [4].

NAFLD-associated HCC, compared to other etiologies, tends to occur later in life, in patients with metabolic and cardiovascular comorbidities [2]. This may help explain why, in patients with HCC and liver cirrhosis, NAFLD patients, as compared to other etiologies, present a worse prognosis [2]. The treatment of those patients is not only jeopardized by older age and comorbidities, NAFLD-associated HCC seems to be less responsive to immunotherapy [5].

Importantly, we are failing to screen these patients, since more frequently than in other etiologies, NAFLD-associated HCC is detected outside specific surveillance [2]. This cannot be justified only by non-cirrhotic HCC, which would fall out of screening programs because it also happens in the context of cirrhosis. Indeed, patients with hepatitis C virus-associated cirrhosis are 2 times more likely to be enrolled in HCC screening programs than patients with NAFLD-associated cirrhosis [6].

Current screening tools perform worse in patients with NAFLD. For example, ultrasound, the basis of the biannual proposed HCC screening protocol, seems to be 3 times more inaccurate to detect HCC in patients with NAFLD-associated cirrhosis compared to other forms of liver cirrhosis [7], as steatosis increases ultrasound attenuation impairing the detection of deep liver nodules. Also, there is a dose-dependent decrease in ultrasound accuracy with increasing BMI [7]. Ultrasound reports should illustrate the possible limitations to visualization according to the US LI-RADS algorithm, which stratifies into minimal, moderate, and severe limitations. Patients with low ultrasound scores would probably benefit from other imaging techniques such as CT and MRI, or the most recently proposed abbreviated MRI protocols. The combination of the ultrasound with alpha-fetoprotein (AFP) seems to increase by 20% the sensitivity of HCC screening. However, in non-hepatitis C virus cirrhosis, a cutoff of 11ng/mL may outperform the classic 20ng/mL cutoff [8]. Clinical-laboratory scores may outperform AFP. One such score, already evaluated in phase 2 studies in NAFLD-associated cirrhosis, is the GALAD that incorporates sex, age, and tumor markers, with an AUROC of 0.90. GALAD score may also be useful to identify patients at risk of developing HCC that would benefit from being enrolled in screening programs since high scores have been detected even 1.5 years before the development of HCC [9].

Taking all into consideration, when deciding to screen patients with HCC, we face the paradox of up to 40% of patients with NAFLD-associated HCC not presenting liver cirrhosis, while, the development of HCC in a patient with NAFLD without cirrhosis is a very rare event. Patients with NAFLD-associated cirrhosis, that is, with liver stiffness measurement (LSM) higher than 15kPa, should undoubtedly be considered for HCC screening, since its annual incidence is higher than the 1.5% cutoff for HCC screening cost-effectiveness in patients with cirrhosis. Noticeably, other factors must be taken into consideration when enrolling patients in HCC screening programs, such as functional status, overall health and appropriateness for HCC treatment if HCC is found. Screening may be more expensive in NAFLD-associated cirrhosis, with a higher need for more sensitive techniques such as abbreviated MRI due to less accuracy of ultrasound in this set. As such, risk-stratification models such as the hccrisk [10] that integrates age, gender, BMI, diabetes-mellitus, platelets count, aminotransferases, and serum albumin, may help identify low risk patients that would not benefit from screening and high-risk patients that would benefit from more intensive screening strategies.

Regarding pre-cirrhotic HCC, universal screening is not cost-effective, the challenge being the identification of high-risk populations. Indeed, non-cirrhotic NAFLD-attributed HCC corresponds to 6% of HCC [2], and considering an estimated global incidence of over 1 million cases by 2025, excluding non-cirrhotic NAFLD patients from screening, would result in 60000 HCC cases per year being missed from screening programs. The most important risk factor for HCC development in patients with non-cirrhotic NAFLD is the presence and severity of liver fibrosis (assessed by histology, non-invasive scores or LSM) [11]. Indeed, current guidelines by European, American and Japanese societies for the study of the liver, already recommend screening in patients with F3 fibrosis. Other risk factors are older age (being exceedingly rare in those younger than 65 years old), the presence of diabetes-mellitus, particularly those with rethinopathy [12], and increased aminotransferase levels [3]. Alcohol intake, even in the social range, is a strong risk factor in

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cirrhotic patients, whereas in non-cirrhotic is controversial, albeit there is a known synergism between alcohol and increasing BMI [13]. As such, probably patients suited to screening would be older than 65 years old, with diabetic retinopathy, increased aminotransferases, and some liver fibrosis.

Polygenic [14] and transcritptome [15] risk scores have shown promising results in stratifying NAFLD patients for HCC risk, even in the pre-cirrhotic state, with the former showing high performance for selecting patients for screening, and the latter for excluding them.

In conclusion, HCC screening in NAFLD patients is failing for 3 main reasons: 1) astonishingly under-diagnosis of NAFLD-associated cirrhosis or advanced fibrosis in the general population, 2) impressive under-screening for HCC in patients already known to have NAFLD-associated cirrhosis, and 3) a high proportion of HCC diagnosed in pre-cirrhotic patients. The first premise could be overcome with an active search for advanced liver fibrosis in high-risk populations such as obese and patients with diabetes-mellitus, as already proposed in AASLD guidelines. The second premise warrants higher awareness from physicians that take care of these patients. Regarding non-cirrhotic NAFLD patients, there is still a need for better stratification tools such as clinical and polygenic scores that accurately identify patients at risk for HCC, so we do not miss 1 in every 20 HCC cases worldwide.

Declaration of interest

None.

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