Editorial

Clinical patterns of hepatocellular carcinoma (HCC) in non-alcoholic fatty liver disease (NAFLD): a multicenter prospective study

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Hepatocellular carcinoma (HCC) is the most common primary malignant tumor of the liver and the fifth most common cancer, ranking third in overall mortality between the various malignancies (1,2). Currently, it is assumed that the incidence of HCC is increasing not only because of the epidemic of hepatitis C, but also is related to the increase in obesity, diabetes and nonalcoholic fatty liver disease (NAFLD), especially in developed countries (3).

NAFLD encompasses a large spectrum of liver abnormalities ranging from simple fat deposition within the hepatocytes without inflammation or fibrosis (simple steatosis), to cases of non-alcoholic steatohepatitis (NASH), cirrhosis and HCC in patients without a history of alcoholism. In the last years, NAFLD is the most common cause of chronic liver disease in the West and have been identified as emergent risk factors for this primary liver cancer (4-6). Besides, nowadays, NAFLD-related cirrhosis (NAFLD-cirrhosis) or NAFLD-related HCC (NAFLD-HCC) are the second cause of liver transplantation in the USA (7). The prevalence of NAFLD-HCC is rising worldwide, especially in Western countries where 4–22% of HCC cases are now attributable to it (8).

Case control studies comparing the incidence of HCC in patients with NASH to patients with HCV provide one estimate of HCC risk in patients with NASH (9,10). However, these studies are limited to single center experiences and describe mostly a small number of patients with NAFLD-cirrhosis followed longitudinally who develop incident HCC. Other longitudinal natural history study provides single center cohort descriptions of incident HCC among patients with all stages of NASH (11,12). These studies, when combined, provide an HCC incidence estimate of about 1.6% over 15 years in patients with NASH (12) and 12.8% over 3 years in patients with NAFLD-cirrhosis.

Ascha *et al*. [2010] identified older age and alcohol consumption as independent risk factors associated with incident HCC in NAFLD-cirrhosis (9), whereas Sanyal *et al*. [2006] did not identify predictive risk factors for HCC in patients with NAFLD-cirrhosis (10).

Another single center experience from the University of Pittsburgh transplant center compared 17 patients with NASH-HCC versus 81 NASH patients without HCC who underwent liver transplantation over a 9-year period (11). No significant differences were found between NASH-HCC versus NASH patients who underwent liver transplantation. However, sample sizes within published studies to date are too limited to draw clear conclusions regarding risk factors for HCC development in patients with NASH.

A recent retrospective, multicenter, case-control study evaluated the risk factors associated with HCC in a cohort of individuals with NAFLD-cirrhosis with and without HCC and demonstrated that male gender, increased age and non-Hispanic ethnicity are associated with HCC in NAFLD-cirrhosis, which was characterized by early stage

disease at diagnosis and treatment with locoregional therapy and transplant (13).

In our group in Brazil some years ago, we identified among 394 patients with HCC detected by ultrasound imaging over 8 years and staged by the Barcelona Clinic Liver Cancer (BCLC) criteria, 7 cases (1.7%) with HCC occurring in the setting of active biopsy-proven NASH, and one without cirrhosis (14). More recently, forty-two patients with HCC related to either to NAFLD or cryptogenic cirrhosis were retrieved retrospectively from 2 centers in Brazil, we observed 4 (10%) patients without cirrhosis. HCC was diagnosed based on noninvasive diagnostic criteria of the American Association for the Study of Liver Diseases in 24 patients (57%). Diagnosis of HCC was confirmed by histology in 18 patients (43%) (15). Differently from that found in our study, in this very interesting multicentric Italian study by Piscaglia *et al.*, (16), a total of 756 patients with either NAFLD [145] or HCV-related chronic liver disease [611], the authors demonstrated as compared to HCV that cirrhosis was detected in 78 of 145 NAFLD patients (53.8%) differently from the near totality of HCV-HCC. Another, Brazilian study, included 110 patients with a diagnosis of HCC and NAFLD from nine hepatology units in six Brazilian states, the patients, with HCC without cirrhosis accounting for 7.7% (17).

Nevertheless, the development of HCC without cirrhosis is a relatively rare phenomenon, only 5% of cases of HCC develop in non-cirrhotic livers, however, some studies have suggested the possibility of the emergence of NAFLD-HCC, without the prior development of cirrhosis (18,19). Thus, despite scientific advances and the implementation of measures for the early detection of HCC in patients at risk, patient survival remains low. Although the risk factors for NAFLD-HCC are already well established, the exact molecular mechanism that leads to the development of HCC is not yet defined. Based on the role that components of Metabolic Syndrome (MS) represents in the pathogenesis of NAFLD and progression to HCC, and considering that the mechanisms are not yet fully clear.

We read with interest the study by Piscaglia *et al.*, (16) because it is the first study that survival was modeled according to clinical parameters, lead time bias and propensity analysis. As compared to HCV, HCC in NAFLD patients had a larger volume, showed more often an infiltrative pattern and was detected outside specific surveillance. Cirrhosis was present in only about 50% of NAFLD-HCC, differently from the near totality of HCV-HCC. Regardless of the tumor stage, the survival was significantly shorter (P=0.017) in patients with NAFLD-HCC, namely 25.5 months (95% CI: 21.9–29.1) than with HCV-HCC, 33.7 months (95% CI: 31.9–35.4). Additionally, to eliminate possible confounders, a propensity score analysis was performed, which showed no more significant difference between the two groups and the analysis of patients within Milan criteria submitted to curative treatments did not show any difference in survival between NAFLD-HCC and HCV-HCC (respectively 38.6 *vs.* 41.0 months, P=n.s.).

The authors demonstrated that NAFLD-HCC is more often detected at a later tumor stage and may arise also in the absence of cirrhosis. However, after patient matching, NAFLD-HCC has a similar survival as compared to HCV-infected patients. Future challenge will be to identify patients with NAFLD who require more stringent surveillance in order to offer the most timely and effective treatment.

Considering the current scenario which demonstrates an increase in the worldwide prevalence of HCC in NAFLD and the most studies are limited to single center experiences, there is an immediate need for further new large multicenter longitudinal studies in attempt to better understand the molecular mechanisms of carcinogenesis in NAFLD, as well how we can manage screening in these patients without liver cirrhosis. The NASH Clinical Research Network (NASH CRN) and other collaborative studies may help to answer these questions in the future.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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