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EDITORIAL

Editorial comment on hepatocellular carcinoma in the noncirrhotic liver: Clinical characteristics and results in Veracruz, Mexico☆

Comentario editorial sobre carcinoma hepatocelular en hígado no cirrótico: características clínicas y resultados en Veracruz, México

The incidence of hepatocellular carcinoma (HCC) has continued to increase and is currently the second most lethal tumor worldwide. Its main risk factor is cirrhosis and the majority of cases across the globe are attributed to the hepatitis B virus, followed by the hepatitis C virus. However, in the Western world, hepatitis C virus is the main cause. Nevertheless, HCC epidemiology is changing, and with access to the new antivirals, the frequency of hepatitis C virus-induced disease is beginning to decrease, whereas cases due to nonalcoholic fatty liver disease (NAFLD) continue to rise.[1] Screening and treatment of HCC patients that present with cirrhosis are based on different levels of evidence in the international clinical practice guidelines. However, up to 20% of HCC cases occur in the absence of cirrhosis, and management is not well stipulated in that scenario, given that the Barcelona Clinic Liver Cancer algorithm, which is recommended in the European and North American guidelines, is designed and recommended for patients with cirrhosis. When there is no cirrhosis, the recommendation is to opt for surgical treatment, whenever possible and viable, but the role of outcome factors, defined by the stages the cirrhotic patients are in, is not clear (i.e., tumor burden, liver function, functional status). In the present issue of the *Revista de Gastroenterología de México*, Martínez-Mier et al. described the clinical characteristics and progression of 33 patients with HCC and no cirrhosis, at a hospital center in Mexico, in an effort to identify outcome factors.[2]

Their study is very important, given the lack of publications on HCC in the absence of cirrhosis in Mexico. In line with other studies, Martínez-Mier et al. reported that 20% of HCC cases at their hospital center presented without cirrhosis. However, we do not have the figures for each of the HCC etiologies, to estimate the percentage of non-cirrhotic cases in each of them. With respect to NAFLD, that percentage has been estimated to be as high as 40-50%.[3] It is particularly relevant that half of the cases corresponded to women, because at the global level, HCC is more common in men, in cases both with and without cirrhosis. Said phenomenon is interesting, given that similar proportions regarding sex distribution have been described in different studies conducted in Mexico on patients with cirrhosis.[4–6] That could be explained by distinctive exposure to risk factors for developing HCC or by greater access to health services on the part of women (reference bias), but it is something that requires in-depth investigation.

Despite the limitations of the operational definition of NAFLD used by the authors, they aptly showed that fatty liver was the risk factor associated with the development of HCC in 64% of the cases, confirming the fact that NAFLD is also the most common cause of HCC, in the absence of cirrhosis, in Mexico.[7] The importance of that finding is underlined because Mexico is emerging as one of the countries with a high prevalence of NAFLD. Unfortunately, there are no clear indications of when to screen patients that do not present with cirrhosis, except in patients with hepatitis B virus. There are currently no guidelines for identifying which patients with NAFLD should be screened, resulting in the diagnosis of HCC at more advanced stages. There are two big problems regarding NAFLD. One is that it is a highly prevalent disease, thus screening all patients would not be

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cost-effective, and the other is that the yield of ultrasound imaging is inferior in obese patients. From the results of the study under discussion, we can conclude that it would be insufficient to restrict screening to patients with advanced fibrosis, because it was not present in the majority of cases. Resolving those challenges would involve 1) identifying a biomarker or prognostic score that would determine which patients had a high enough risk for HCC so that screening would be cost-effective, which would probably include clinical and genetic variables,[8] and 2) exploring other more sensitive screening methods, e.g., based on abbreviated magnetic resonance protocols with non-contrast-enhanced sequences.[9] Regrettably, the study did not include a control group, so factors associated with the development of HCC without cirrhosis could not be analyzed. Among the factors that have been described in other studies are NAFLD, the different components of metabolic syndrome, alcohol consumption, male sex, and FIB-4.[10–12]

The article contributes very pertinent information on the analysis of HCC in Mexico, but it has some limitations that should be addressed. The study did not include a comparative group of patients with HCC of the same etiology and cirrhosis. That would have enabled knowing whether the characteristics observed in the study were those of HCC in Mexico in general, such as female sex, or whether they strictly reflected the particular case of HCC, with no cirrhosis. Another limiting factor was that by having included patients with advanced fibrosis, there was the possibility that the sample was ''contaminated'' by cirrhosis. If, strictly speaking, the advanced fibrosis was not cirrhosis, it could form part of the so-called compensated advanced chronic liver disease (cACLD), which refers to a continuum between the pre-cirrhotic patient and the compensated cirrhotic patient. A very thin line separates the two, given that both stages behave practically in the same manner. Hence, the European guidelines recommend screening for all patients with F3, and the American Gastroenterological Association particularly recommends screening in patients with NAFLD and advanced fibrosis.[13] In addition, of the 7 patients that did not undergo biopsy, we do not know if they had advanced fibrosis determined by FIB-4. Likewise, 20% of the patients had probable advanced fibrosis scores, and we do not know how many of them did not have a biopsy.

Even though mean survival was similar to that of other studies, and survival in the patients that underwent resection was superior to that described in other study samples (probably the result of a very conservative selection of surgery candidates), the very poor survival rate in the patients that received local treatment was striking, even lower than the survival rate we see in patients with cirrhosis. Perhaps local treatment was used solely in patients that not only were not candidates for surgical treatment due to comorbidities, but also that had poor outcome factors. However, no conclusions can be drawn because the characteristics of the patients that underwent the different treatments were not described. In relation to the factors associated with survival, the results produced by the multivariate Cox model should be cautiously interpreted. It would be erroneous to consider there were no associated factors, given that the majority of studies have found associations between mortality and the variables of age, tumor burden, satellitosis, or hepatectomy dimensions.[14–16] The study most likely did not have the number of outcomes needed, or enough power, to include a multivariate analysis. Notwithstanding, in the absence of cirrhosis, it is unlikely that noninvasive fibrosis markers would play an important role because outcome is more the result of tumor burden. That is similar to what we see in patients with compensated cirrhosis and no portal hypertension, in which there is no competitive event on the part of liver dysfunction, and outcome is the result of the HCC itself. Nevertheless, unlike other case series in which tumor burden is the most relevant outcome factor in the absence of liver dysfunction,[7,12] it had no prognostic value in the study by Martínez-Mier et al. One explanation could be the small sample size or the manner in which the authors evaluated tumor burden. Except for tumor size, they did not analyze the number or distribution of tumors as independent variables, but rather as one of the items in the systems designed for patients with cirrhosis, such as the Okuda and CLIP criteria.[16]

Finally, some data need a fuller description to be adequately interpreted. For example, in the patients with ''thrombus'', whether they presented with soft thrombus or tumor thrombus was not specified, nor was it clear why synthetic liver function (i.e., ALBI) in the patients with no cirrhosis was compromised. The circumstances that led to the diagnosis of HCC, such as whether some of the patients underwent screening (e.g., those that had advanced fibrosis), whether they had symptoms, or whether they were cases of incidental findings, were also not established, which would have inevitably had an influence on the disease stage at presentation.

In conclusion, the study by Martínez-Mier et al. reinforces the importance of having tools for determining the individual risk for developing HCC, particularly for patients with NAFLD. Of those tools, screening should be directed and cost-effective, given that only through its effective performance can the morbidity and mortality rates of those patients be improved by detecting early and curable forms of HCC. With respect to treatments for HCC with no cirrhosis, the study confirms that surgery should be performed whenever possible, with regional treatments carried out exclusively for non-resectable cases.

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Conflict of interest

The author declares that there is no conflict of interest.

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