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**Hepatitis B virus-associated hepatocellular carcinoma is still a matter of concern
in the French Caribbean Island of Guadeloupe**

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Abbreviations HBV, hepatitis B virus; HBsAg, HBs antigen; HCC, hepatocellular carcinoma;
CHB, chronic hepatitis B; HBV-VL, HBV viral load; SVR, sustained virological response; AFP,
Alpha-fetoprotein.

In the 1990's, Guadeloupe, a French Caribbean Island, was classified as a territory intermediate prevalence for hepatitis B virus (HBV) with about 3% of hepatitis B surface antigen (HBsAg) carriage [1]. Such a prevalence may likely be related to the unique settlement pattern of the Island, as Guadeloupe has been at a crossroads between Africa, Europe, India and the Americas because of the slave trade (17th-19th centuries), followed by an important immigration of Indian and West African workers. Indeed, molecular analyses of viral strains that are spreading in the neighboring island of Martinique, sharing a strict similar settlement pattern, demonstrate that these populations originated from highly endemic regions for HBV, came with their viruses [2].

The last past ten years, HBV prevalence has decreased from 3% to 1.5% [3], due to the effectiveness of anti-HBV vaccination campaigns and to systematic screening of HBV status of the women during pregnancy and thus, preventing mother to child transmission [4]. However, HBV remains the first cause of hepatocellular carcinoma (HCC) in Guadeloupe, with a standardized incidence of 3.6 and 2.0 per 100,000 persons per year in men and women, respectively [5 personal communication,6]. In addition, the mortality rate also remains high despite a better access to antiviral therapies. Of note, HCC incidence is two-fold higher in other Caribbean islands with 6.1 and 4.5 per 100,000 persons per year in men and in women respectively [7].

Thanks to a retrospective comparative study of a cohort of 25 patients from Guadeloupe and 80 ones from Lyon (in Metropolitan France), followed from 2004 to 2018 in their respective reference center, this study is the first one describing the main clinical and biological features of the HBV associated HCC in the Caribbean island of

Guadeloupe. The comparison of these two cohorts of patients highlighted several main features in clinical presentation and management of HCC.

First of all, at the time of HCC diagnosis, only a small proportion of Guadeloupean patients had been treated for chronic HBV infection (CHB). Indeed, very often, the diagnosis of CHB and HCC were concomitant in Guadeloupe and as a consequence, HCC were found at more advanced stages in HBV carriers, with elevated transaminases and high levels of HBV viral load (HBV-VL) (in 40% vs. 20%, $p=0.04$) and patients were globally less virosuppressed than those of Lyon's cohort (in 8% vs. 49%; $p=0.0001$). A previous meta-analysis study by Sung and collaborators, clearly showed that either IFN or nucleos(t)ide analog treatments significantly reduced the risk of HCC in CHB patients [8]. In another more recent study, Kim JH et al., showed that HCC occurred more frequently in patients with low level of viremia by either persistent or intermittent episodes of $> 2,000$ IU/mL detectable HBV-VL, compared with those having a sustained virological response (SVR) undetectable HBV-VL, while under entecavir treatment [9]. Moreover, in the recent prospective CIRVIR cohort study, Brichler et al. showed a similar HCC incidence in cirrhotic patients with or without SVR, but with more aggressive forms in the latter group [10]. In our Guadeloupean cohort, a high proportion of patients (more than 40%) had HBV VL $>2,000$ IU/mL and also high Alpha-fetoprotein (AFP) serum levels (44% more than 1,000 ng/mL) at diagnosis of HCC. These patients were mainly cirrhotics (in 76%), but only 37% of them had an antiviral treatment. They were out of the Milan criteria (88%) and only 20% of them eligible for anti-HCC curative treatments. Unfortunately, in this retrospective study, we did not have access to the natural history of the disease for the patients. Indeed, almost all patients had no strict follow-up for their HBV-infection and consequently, a lack of

regular screening for HCC, as recommended in the French prospective CIRVIR cohort [10].

It is now established that common comorbidities such as diabetes mellitus, alcohol or obesity do increase the risk of liver cirrhosis, while the burden of these comorbidities and their impact on HCC are not well defined [11, 12] Brichler et al. [10] also confirmed that age >50 years, BMI > 30 and platelet count <150,000 were risk factors for the occurrence of HCC. The design of our study doesn't allow us to establish a link between HCC and these comorbidities due to the limited number of patients. However, we observed that alcoholism was frequent in non-cirrhotic Guadeloupean patients (33%) and could probably be a co-factor in carcinogenesis and lack of follow-up. Consequently, alcohol intake and obesity must be taken into account by the physician to improve the follow-up and the screening of HCC.

HBV genotypes could be associated with a severe presentation and a rapid progression of HCC, as reported for HBV American F genotypes [13]. Unfortunately, we could not have this data for our patients, but we are going to start a prospective study to consider this.

Theoretically, survival for cancer patients depends on access to appropriate treatments, which is closely linked to the economic capability and healthcare policy of individual countries. However, this study shows a poor prognosis of HCC in affected patients of Guadeloupe. This study highlights the needs for the public health authorities to greatly improve the management of HBV chronic infection in order to allow access to anti-HBV (when needed) and curative anti-tumoral treatments and to lead to significant impact on HCC burden in Guadeloupe. Our results also argue for an active screening for HBV chronic infection in Guadeloupe but also in other Caribbean islands, where the prevalence of chronic carriage of HBV remains much higher than in Europe.

In conclusion, this study shows a poorer prognosis of HCC in the University Hospital of Guadeloupe, with more advanced forms at diagnosis and less frequent decisions of curative treatments in patients, implying the urgent implementation of the main international recommendations on this topic.

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