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Editorial

Hepatitis B and C viruses and hepatocellular carcinoma

In the last few decades, innovations in science and technology have spurred basic and clinical research on hepatitis B (HBV) and C (HCV) viruses; both fields have made substantial contributions to public health. On the one hand, advancements came from the more specific serological immunoassays and highly-sensitive molecular diagnostic tests paralleled by a deeper comprehension of the viruses' genetic structure and life cycle, combined with the manufacturing of HBV vaccines, new anti-HBV antivirals capable of very efficiently inhibiting viral replication, and the new anti-HCV direct-acting agents (DAAs) [1,2]. On the other hand, epidemiological studies have clearly shown that hepatitis virus infections may have different clinical outcomes [3], ranging from acute hepatitis to cirrhosis and, in some cases, to hepatocellular carcinoma (HCC). Until now, vaccination coverage and antiviral therapies have been the most potent frontline armamentaria available to avoid the long-term clinical consequences of these viruses. However, this story has not ended because about 300 million people live with chronic hepatitis B and 75 million are chronically infected with hepatitis C worldwide [4]. Thus, the World Health Organization aims to eliminate viral hepatitis by 2030, hopefully having a substantial impact on HCC prevention [5]. However, such a desirable objective may not be reached in countries with lower socioeconomic development, such as Latin America or other continents [6].

This special issue, "Hepatitis B and C Viruses and Hepatocellular Carcinoma," covers specific aspects of the epidemiology of these viruses as the leading etiological factors for the development of HCC, the role of regional environmental factors, the risk of HCC after antiviral treatments, the outcome after non-surgical resection of HCC, and the study of the molecular mechanisms leading to this pathology.

Opening this special issue, L. Quiroz and S. Roman's article tells us about the role of genetic and environmental risk factors causing chronic liver damage in Mexico. The role of viral genotypes, host gene polymorphisms, consumption of a hepatopathogenic diet, diets rich in cholesterol, and aflatoxins are described while emphasizing the regional differences of these factors and their impact on the development of HCC.

Next, from Italy, F. Trevisani and E. Giannini present the in-depth analysis of a 20-year systematic collection of clinical data achieved by the ITA.LI.CA Consortium in Italy. The article offers a great display of how national clinical databases are relevant for obtaining reliable information from real-world experience and how this process can speed up the rate of our know-how providing a different perspective about the progresses achieved in the study of HCC. Furthermore, beyond the extensive national epidemiological study surveys, understanding the *in situ* condition, i.e., what is going on in terms of hospital admissions within a specific region and the contributing risk factors, can aid in developing future elimination strategies for viral hepatitis. Also in this issue, I. Cacciola et al. point out the importance of detecting viral hepatitis and liver damage in a quite large cohort of asymptomatic Italian patients with no history of liver injury hospitalized in Internal Medicine or Surgery Divisions because of clinical conditions unrelated to hepatological diseases. Given the new trends of artificial intelligence, these studies are examples of what can be achieved in other regions like Latin America.

Similarly, S. Laguna et al. evaluated the presence of viral hepatitis in one of the largest public hospitals in western Mexico and found a higher frequency of viral hepatitis-related liver damage than reported in national studies. Among the study group, anti-HCV was prevalent in 3% and HBsAg in 1%. In contrast, patients who were negative to these markers, 10% had abnormal transaminases and significant liver fibrosis, indicating that occult hepatitis B or other etiologies of liver damage may be prevalent. Strikingly, in this study, patients tested for viral infections or liver damage were diagnosed by different hospital services suggesting the need to establish strategies for early detection of these conditions.

The subdiagnosis of viral hepatitis is confirmed at the national level in Mexico with the study by M. Carnalla et al., who documents a prevalence of HBV infection of 0.5% in 2,280 serum samples obtained from the 2018 National Health and Nutrition Survey. These data are of great significance since this reported prevalence is higher than previously estimated despite the introduction of the anti-HBV vaccination in January 1999.

Altogether, these studies show that the problem of HBV subdiagnosis is when HBsAg, as the only marker, is used. In the case of Mexico, HBV genotype H clinically manifests with a very low viral load that frequently causes an occult hepatitis B status leading to underdiagnosis [7,8]. Thus, routine diagnostic tests should include anti-HBc antibodies and molecular tests in most patients with risk factors. On the other hand, the national HBV vaccination strategies and their effect on HBV control should be analyzed and re-evaluated to confirm their effectiveness.

In contrast with the large-scale epidemiological surveys, different results can be found when these studies are carried out in more specific regions, such as rural areas, compared to urban areas. The study by K. Chan and N. Manglian reports the prevalence of HCC and risk factors from 2014 to 2018 in rural Northeastern USA, observing a 2-fold increase in HCC prevalence and an increment in intravenous drug abuse, making it clear that prevention strategies for viral hepatitis should be regionalized.

The following study is presented by F.G. Villamil et al., who excellently documented the effectiveness of a micro-elimination plan in the small town of O'Brien in Argentina. By treating with antivirals from two different eras, pegylated-interferon/ribavirin at first and later the DDAs, they achieved a 20-fold decrease of HCV prevalence

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after the initial outbreak in 1999. Using molecular tools, they identified the source of HCV infection, the natural history, risk factors and documented the impact of antiviral treatment in this 20-year follow-up study.

Next, T. Queiroz Reuter et al. carried out a molecular epidemiological study in the southeast state of Espírito Santo in Brazil, finding a differential distribution of two HBV genotypes. HBV A1 was predominant among a subpopulation where the infection was acquired by mother-to-child transmission, whereas genotype D3 was common across individuals infected by intrafamilial transmission. Furthermore, P. Oliveira Gionda et al. present an article detailing the next-generation sequencing method and - most importantly - the phylogenetic analysis of complete HBV genotypes F and H genomes, the most endemic HBV sequences among the Latin American populations. These studies highlight the role that molecular diagnostics and sequencing provide for the clinical management of viral hepatitis diseases in this world region.

Towards the end of our special issue, C. Celsa et al. present a critical appraisal regarding the evidence of the effect of DAAs on the risk of HCC development which is an ongoing hot topic. The Authors carefully dissected essential and controversial aspects of the occurrence/recurrence of HCC in chronic hepatitis C infected patients treated with DAAs and the efficacy of these drugs on overall survival in patients with HCV-related early-stage HCC. Next comes S. Wei et al.'s study, which compared the rate of overall survival and progression-free survival between HCC Child-Pugh A patients undergoing anatomical resection and non-anatomical resection, finding that portal vein invasion and tumor size > 5 cm were risk factors for worse prognosis after hepatectomy, not related to the surgical approach.

Closing this special issue are three basic studies linked to the world of microRNAs (MiRs) and their potential use as prognostic markers and therapeutic targets in HCC. In X. Liu et al.'s study, the oncogenic role of miR-3682 was analyzed in HCC tissues, showing that it exerts an inhibitory effect on the AMPK signaling pathway by negatively regulating ADRA1A, thus promoting a malignant phenotype. F. Rengen et al., working with oncogene miR-211-3p, showed that it regulates the HCC cell proliferation, migration, and invasion via the LIFR pathway. Finally, W. Honggang et al. present a study in an HCC mice model regarding the function of long intergenic non-protein coding RNA 1006 (LINC01006), showing that downregulation of this sequence represses the development of HCC by sponging miR-194-5p and modulating the expression of the cell adhesion molecule CADM1.

In conclusion, thanks to the contribution of several important groups of research, this special issue shows that HBV and HCV - the leading causes of HCC development - are still highly prevalent in different areas of the world. HCC incidence is also growing worldwide due to hepatitis virus infections and metabolic disorders, including obesity, diabetes, and dyslipidemia [9]. In this sense, several articles provide scientific information and indicate methodological approaches beneficial for better dealing with this threat for public health. Furthermore, they highlight the need for more prospective and large-scale studies to provide updated scientific data registering the regional background factors influencing the development of HCC. The take-home message is that sound scientific research in hepatology is the basis to build clinical practice guidelines with a personalized medicine approach consistent with the needs and characteristics of the affected populations to ameliorate the impact of liver diseases [10,11].

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