Letter to Editor

# Shedding light on the "gray zone": Hepatic fibrosis in chronic hepatitis B patients with fluctuating HBV DNA levels

Sir,

Management of chronic hepatitis B (CHB) patients with fluctuating HBV DNA levels remains a challenge, as the natural history of their disease is not as well-defined; thus, the best management strategy is unclear. In the most recent American Association for the Study of Liver Diseases (AASLD) CHB guidelines, HBeAg-negative patients are divided into CHB and inactive CHB, with the differentiating variable being transaminase levels and HBV DNA levels, with 2,000 IU/ml being the cut-off, and treatment is based on level of HBV DNA and ALT elevation. Patients in the "gray zone" are monitored and treated if transient elastography is greater than or equal to F2.[1] European Association for the Study of the Liver (EASL) guidelines in 2009 had similar criteria, using the terminology HBeAg-negative chronic hepatitis and inactive carrier, and had similar treatment criteria.[2]

In 2018, Bonacci *et al.*[3] described long-term outcomes of Caucasian patients with CHB in the absence of treatment; 40% of gray zone patients transitioned to inactive carriers during the median 8.2-year follow-up and DNA fluctuations inversely correlated with this transition. This result has been used as evidence for an active monitoring strategy in these gray zone patients.[4]

We read with interest the article by Sanai and colleagues who evaluated the presence of F2-F4 fibrosis in this subclass of CHB patients.[5] This article provides prospective data on this patient population which is not described elsewhere in the literature. Two hundred and thirty-four CHB patients without decompensated cirrhosis, significant alcohol intake (>20 g/day) or comorbid liver disease were identified, of which 73 (31.2%) had HBV DNA fluctuation. The presence of F2-F4 fibrosis was lower in the fluctuating group compared to nonfluctuating patients, but not statistically significant (8.2% vs. 18%, $P = 0.052$). These data suggest that these patients with fluctuating HBV DNA may be classified as inactive CHB as far as disease-natural history, monitoring and management strategies are concerned.

Both AASLD and EASL guidelines do recommend routine monitoring of ALT and HBV DNA in close intervals, but these intervals have not been able to mirror inactive CHB monitoring strategies as suggested by this investigation. Limitations of this study include the relative homogeneous patient population and the exclusion of comorbid liver disease, which may limit generalizability to clinical practice. Given that not much data exists in this population, we believe that further studies to confirm these findings will be helpful to ensure that this clinical scenario is more fully understood.


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## Conflicts of interest

There are no conflicts of interest.


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