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Reviewer#1:

SPECIFIC COMMENTS TO AUTHORS

The manuscript lacks of the reference section; please add the references, so that the revision process could be properly performed. As specific comment, the authors stated that HBcrAg may not be an ideal marker in HBeAg negative CHB patients. Several studies support its use in these patients; see PMID: 33525443 and 33465257. In addition, given the low analytical sensitivity, I have some concerns on its possible usefulness in patients/subjects with occult HBV infection. In a recent manuscript, authors observed HBcrAg values below 2.0 log in HBsAg-negative/anti-HBc-positive liver donors irrespectively from the presence or absence of intrahepatic HBV cccDNA (PMID: 29621551)

Reply

The reference section has been added. The point is well accepted.

Reviewer#2:

SPECIFIC COMMENTS TO AUTHORS

I read this letter carefully, but I don't understand the author's true thoughts. In the life cycle of HBV, cccDNA combines with histones to form HBV minichromosomes. They play two roles, one part is stored in the nucleus of liver cells, and the other part is transcribed into pregenomic RNA and mRNA. Therefore, I cannot understand the connection between cccDNA and HBcrAg. Reading the first paragraph, I do not agree with the author's conclusion, 'even on antiviral treatment, HBcrAg can reflect cccDNA activity in hepatocytes'. On the contrary, my conclusion is that HBcrAg can not reflect cccDNA activity in hepatocytes. In addition, in the last paragraph of the letter, the author also believes that HBcrAg, as a marker, has three critical defects. Suggestion: re-submission after revising manuscript.

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Reply

The intrahepatic cccDNA transcribes into pregenomic RNA and precore mRNA. The precore mRNA further translates into HBcrAg (HBeAg, HBcAg and p22cr Ag). Therefore, HBcrAg directly reflects intrahepatic cccDNA levels. This has been explained in detail in first paragraph.

Reviewer#3:

SPECIFIC COMMENTS TO AUTHORS

As a promising novel serum marker, HBcrAg has been increasingly paid attention to. The author discussed the origin, composition, clinical significance and so on, and put forward some problems that need to be discussed in the original paper, for example, different treatment schemes (NAs and PegIFN) may cause bias in results and analysis. At last, author pointed out many issues about HBcrAg. I agree to publish this manuscript.

Reply

Thanks for your comments.

Reviewer#4:

SPECIFIC COMMENTS TO AUTHORS

This review evaluates the research value of the manuscript for HBcrAg and presents issues such as low detectable rates in clinical practice, possible not an ideal marker in patients with negative HBeAg CHB, and can be found in 40% patient with HBsAg seroclearance, and so on.Which are very objective and informative, and I really agree with these points. On my opinion, It is still controversial for HBcrAg as a potential serological markers of chronic hepatitis B infection and activity. It may be of more predictive value if the subjects

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are limited to certain specific population, such as HBeAg-positive patients.

Reply
The comments are well accepted.

Re-reviewer#1

SPECIFIC COMMENTS TO AUTHORS
I still disagree with the author's answer, The intrahepatic cccDNA transcribes into pregenomic RNA and precore mRNA. Then precore mRNA further is translate into HBcrAg (HBeAg, HBcAg and p22cr Ag). Therefore, HBcrAg indirectly reflects precore mRNA, how can it reflect cccDNA.

Reply
The intrahepatic cccDNA transcribes into pregenomic RNA and precore mRNA. The precore mRNA further translates into HBcrAg (HBeAg, HBcAg and p22cr Ag). Therefore, HBcrAg directly reflects intrahepatic cccDNA levels. This has been explained in detail in first paragraph.

Re-reviewer#2:

SPECIFIC COMMENTS TO AUTHORS
The authors improved the manuscrip according to the comments raised. I suggest to add in line 16, that "HBcrAg can reflect cccDNA quantity and activity in hepatocytes" (PMID: 32008810 and PMID: 30529504). Furthermore, please check reference numbers in the References section.

Reply: The required changes have been done.