Dear reviewers:

Thank you very much for your issues. We have studied the valuable comments from you. Based on your comment and request, we have made extensive modification on the original manuscript:

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: 1 Title. Ok 2 Abstract. The abstract summarizes and reflect the work described in the manuscript. 3 Key words. The key words must be described according to the MeSH Terms. "Hepatitis B Surface Antigens" instead of "HBsAg" "Hepatitis B e Antigens" instead of "HBeAg" 4 Background. Ok 5 Methods. #Patient selection criteria should be better described: - Were patients who consume alcoholic beverages included? What was the limit of daily alcohol intake allowed to include the patient in the study? - Were patients with steatosis excluded? - Why was there no inclusion of patients treated with tenofovir? - How many patients were excluded? Were there any patient losses during follow-up? Consideration should be given to using of a flow diagram. # In Table 1, it would be interesting to describe separately the number of patients who used lamivudine or adefovir dipivoxil. 6 Results. The results of the research are interesting and intriguing. 7 Discussion. Do the authors believe that different Elisa kits for dosing sPD-1levels can contribute to discrepant results in similar studies? Authors should comment on this in the discussion discussion. 8 Illustrations and tables. ok 9 Biostatistics. ok 10 Units. ok 11 References. ok 12 Quality of manuscript organization and presentation. ok 13 Research methods and reporting. Why did the authors use the ARRIVE Guidelines? Did the authors use STROBE Statement? 14 Ethics statements. ok

Reply: Thanks for the valuable comments. We have rewritten the methods and discussion part with the help of experienced authors. Details as follows:

1.Key words were modified according to comments.

2. Methods. We have rewritten the methods part and described the selection criteria of patients. Patients who consume alcoholic beverages were excluded. Patients with steatosis were also excluded according to ultrasound (US)[1]. Patients in this study started their antiviral therapy on 2007, when TDF has not been public used in Mainland China yet. So, there were no patients treated with tenofovir. A total of 53 patients were excluded, 16 of them lacked sequential serum samples or clinical information during follow-up. And we have drawn a flow diagram in Figure 1. We have described separately the number of patients who used lamivudine or adefovir dipivoxil in Table 1.

3.Disscusion.Different Elisa kits for dosing sPD-1 levels can contribute to discrepant results in similar studies. And we have rewritten the discussion part to discuss that. Xia's and Zhou's research used different Elisa kits for dosing sPD-1 levels. There was a significant correlation between the sPD-1 levels and ALT levels at baseline in Zhou's research[2], but a weak correlation in Xia's study[3]. And we have rewritten the discussion part to discuss that.

4. We used the STROBE Statement and the manuscript was prepared and revised according to the STROBE Statement-checklist of item.

Reviewer #2:

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: 1 Please refer to the following literature,After anti-viral treatment, serum SPD-1 levels and SPD-L1 levels were decreased rapidly. Lower baseline SPD-1 levels were associated with Hbeag clearance After 2 years of anti-viral treatment in HBeAg-positive chronic hepatitis B patients. Then both SPD-1 and SPD-L1 levels are recommended for analysis in this study. 2 This study confirmed that The sPD-1 levels were higher in patients with HBsAg loss than in those without HBsAg loss;The sPD-1 levels were negatively correlated with HBsAg levels; This is almost the opposite of the above research, which is strange. 3 The sample size of this study is small, and the results of Cox analysis are almost meaningless and not reliable.The correlation coefficient in correlation analysis is also very small. 4 Statistical analysis should clarify whether sPD-1 level at baseline predicts HBsAg loss or sPD-1 level during treatment predicts HBsAg loss. For example, the summary section, which part of the data predicted HBsAg loss is not explained in detail. [1] Xia J, Huang R, Chen Y, et al. Profiles of sPD-1 and sPD-L1 in chronic hepatitis B virus infected patients with different disease phases and after treatment. Alimentary Pharmacology& Therapeutics. 2020 Jun 51(11):1180-1187.

Reply: Thanks for the valuable comments. We have rewritten the results and discussion part with the help of experienced authors. Details as follows:

1. Thanks for the valuable comments. We have rewritten the discussion part refer to that study. Thank you for your recommendation, we will explore the sPD-L1 for further research in the next study.
2. Thanks for the valuable comments. We have rewritten the results and discussion part. Consistent with Xia's research, our results showed that the sPD-1 levels decreased after baseline and were positively correlated with ALT and HBV DNA levels at 6 and 12 months[3]. Xia's research showed that lower baseline sPD-1 levels were associated with HBeAg clearance after 2 years of antiviral treatment in HBeAg-positive chronic hepatitis B patients. In our study, the baseline sPD-1 levels showed no significant correlation with HBsAg, serum HBV DNA or ALT levels. After 6 months of antiviral treatment, the AUC of sPD-1 for HBsAg loss after 144 months was 0.898 ($p = 0.000$, Figure 4B), whereas that of HBsAg was 0.617 ($p = 0.419$). And the cut-off value of sPD-1 was set at 2.34 log pg/mL, the sensitivity and specificity were 100% and 66.7%, respectively. Therefore, we have explored the value of sPD-1 levels at different time points.
3. Thanks for the valuable comments. We have rewritten the results part.

4. Thanks for the valuable comments. We have rewritten the results part. We found that sPD-1 levels at 6 months had higher AUC values than HBsAg associated with HBsAg loss after 144 months.

1 European Association for the Study of the L, European Association for the Study of D, European Association for the Study of O. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol. 2016: 1388 [PMID: 27062661 10.1016/j.jhep.2015.11.004: 10.1016/j.jhep.2015.11.004]

2 Zhou L, Li X, Huang X, Chen L, Gu L, Huang Y. Soluble programmed death-1 is a useful indicator for inflammatory and fibrosis severity in chronic hepatitis B. J Viral Hepat. 2019: 795 [PMID: 30578715 10.1111/jvh.13055: 10.1111/jvh.13055]

3 Xia J, Huang R, Chen Y, Liu Y, Wang J, Yan X, Zhang Z, Wu C. Profiles of serum soluble programmed death-1 and programmed death-ligand 1 levels in chronic hepatitis B virus-infected patients with different disease phases and after anti-viral treatment. Aliment Pharmacol Ther. 2020: 1180 [PMID: 32363582 10.1111/apt.15732: 10.1111/apt.15732]