We would like to thank the reviewers for their appreciative words as well as the constructive criticisms given to our manuscript. We carefully considered each comment and updated our work accordingly. Please see our point-by-point responses below.

Reviewers' Comments:

Reviewer #1:

It is an interesting a Review about “Chronic hepatitis B infection with concomitant hepatic steatosis: current evidence and opinion”. My concern is determined in the following points.

Point #1 In patients with NASH, liver fibrosis is the main determinant of mortality. In fibrosis development in NASH, triggers and consequences of hepatocytes-macrophage-hepatic stellate cell crosstalk is focused; pathways through which stressed and dead hepatocytes instigate the profibrogenic crosstalk with hepatic stellate cell and macrophages, including the reactivation of developmental pathways such as TAZ, Notch, and hedgehog; how clearance of dead cells in NASH via efferocytosis may affect inflammation and fibrogenesis.

Response:

Thank you for the suggestion. We have added these statements. Now we state: *In the development of fibrosis in NASH, sustained lipotoxicity and endoplasmic reticulum stress induces cell death of steatotic hepatocytes. Developmental pathways including Notch, Hedgehog and YAP–TAZ are persistently activated to cope with the chronic insult. As a result, the crosstalk of hepatocytes-macrophage-hepatic stellate cell and the activation of resident Kupffer cells would lead to inflammatory and fibrogenic responses.* (in Section 2.2)

Point #2 Patients with CHB and liver steatosis should be closely monitored, irrespective of their viral load.

Response:

We agree with the reviewer. Now we have added these statements in the Section 2.1: *Comprehensive assessments and close monitoring are required in the management of CHB patients，irrespective of their viral load.*

Point #3 Proinflammatory Cytokines in NASH: Insulin resistance, in the setting of obesity, is characterized by low-grade inflammation that is associated with macrophage activation with release of proinflammatory cytokines including TNF-alpha and IL-6. TNF-alpha interacts with the NF-k-beta to promote apoptosis, inflammation, proliferation, and angiogenesis. IL-6 activates the signal STAT3, which promotes cell growth and differentiation. Above mentioned should be referred to.

Response:

Thank you for the suggestion. We have added the statements in Section 1.2: *Chronic inflammatory processes are activated in obesity, diabetes and other insulin-resistant states. In this context, activated macrophages release tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), which lead to low-grade adipose tissue inflammation and even the progression of hepatic damage. These proinflammatory cytokines plays a crucial role in liver inflammatory responses through promoting apoptosis, proliferation, angiogenesis and cell growth/differentiation.*

Reviewer #2:

This is a well-written article that comprehensively reviewed the relationship between HBV infection and hepatic steatosis. However, it would be better if some parts of the article are revised prior to publication.

Point #1 Section 1.1 Explain in more detail for the readers on which clinical metabolic profiles, and in what extent, have been reported so far to be associated with the development of steatosis in CHB patients.

Response:

Thank you for your helpful suggestion. We have added the information about associated metabolic profiles. Now we state: *It was reported that overweight (OR*

5.99), hypertriglyceridemia (OR 2.95) and type 2 diabetes (OR 1.88) were risk factors for hepatic steatosis in CHB patients. in the Section 1.1.

Point #2 Sections 1.2 & 2.1 & 2.2 & 2.3 In these sections, conflicting evidences are suggested in a mixed-up manner which may lead to confusion of the readers. Please re-organize the contents for clarification. For example, in the order of pros – cons – the authors' overall stance in each section based on evidences to this date.

Response:

Thank you for your comments. we have revised the confusing statement in Sections 1.2, 2.1, 2.2 and 2.3 accordingly (highlighted in the manuscript). In Section 1.2, we revised the statement about insulin resistance in paragraph 2; In the Section 2.1, we revised the statement in the last paragraph. In Section 2.2, we added the discussion about the mechanisms of fibrosis involved in NASH, and revised paragraph 2-3. In Section 2.3, we revised the statement about HCC and simplified the expressions.

Reviewer #3:

HBV and liver steatosis are two common etiologies of liver diseases. These two etiologies may be presented in the same patient. This review aims to understand the prevalence, out come and mechanism of these two diseases. The review is extensive and well organized. However, many literatures presented with controversy views. The readers may be unable to catch a clear concept.

Comments:

Point #1. In 1.1 prevalence and incidence of steatosis, the meta-analysis (13) and a study using proton-MRS showed a lower prevalence of NAFLD in CHB than in the control (14). These reports seem to be consistent. On the other hand, the incident of NAFLD showed controversy results. As a matter of fact, incidence of steatosis was significantly lower in CHB than in the control (40.6 vs 43.5 per 1000 person-years) in a Korea study (15). The reviewers compared the incidence of liver steatosis in an HBsAg carrier cohort from China (63.89 per 1000 person-years) with a meta-analysis

from general population (overall 52.34 per 1000 person-years). They concluded that incidences of steatosis were similar. The later reference by Younossi ZM et al was not cited. This will make the reader think that these data were from the same study. In my point of view, different incidences from difference studies are difficult to be compared. Therefore, it will be more appropriated to conclude that the incidence of steatosis is lower in CHB than in the normal control.

Response：

Thank you for your comments. We have revised the statement about the comparison of NAFLD prevalence between general population and CHB patients, and we also added the citation of Younossi et al's study. In addition, we have revised the meta-analysis in the review by adding more well-designed recent studies.

Now we state in Section 1.2: *Nine studies addressed a negative association with a possible risk for steatosis in CHB (pooled OR 0.81, 95% CI: 0.71-0.920, P=0.001, Figure 1). Cohort studies also added more information on NAFLD incidence in CHB patients. In a Korean cohort study, the incidence of steatosis was significantly lower in CHB than in the control (40.6 vs 43.5 per 1000 person-years), which was also lower than that of general population from meta-analysis (52.34 per 1,000 person-years).*

Point #2. In 1.2 the metabolic disfunction in CHB, the risk ratio of DM in HBsAg carriers were 1.23-1.90 (31-33). The risk of DM seems to be increased but difficult to be explained when there is a lower risk of steatosis in CHB. The reviewer mentioned 'In subgroups with older age or severe obesity, CHB patients no longer had higher risks of developing diabetes (32)'. This may be misleading. The true is after control of age, BMI and other factors, the risk of DM is higher in non-HBsAg carriers than in HBsAg carriers. In the reference 32, the risk of DM was not high in CHB after removed patients with liver cirrhosis. Liver is an important organ in glucose homeostasis. DM will occur mainly in CHB with decrease functional reserve of liver.

Response：

We have removed the confusing statement of "*The risk ratio of developing new-onset diabetes in HBsAg-positive patients ranged from 1.23-1.90 according to recent cohort studies.*" Second, we revised the second paragraph of Section 1.2. Now we state: *However, numerous studies have revealed a negative association of hepatitis B and steatosis, the risk of insulin resistance is not always parallel. First, decrease liver functional reserve would promote insulin resistance. As one of the principal organs involved in glucose metabolism, liver damage due to hepatitis would cause glucose metabolism disorders. The risk of developing diabetes was decreased in CHB after exclude patients with liver cirrhosis. Second, the association of insulin resistance and steatosis could be attenuated by multiple factors other than viruses. Age and obesity were both confounders of risks of developing diabetes in CHB patients.*

Point #3. In 2.1 disease severity of CHB with NAFLD, there is no doubt that a patient with chronic hepatitis B and NASH will have a poor outcome. The key point of progression will be the inflammation activity. Inflammation induces by either HBV or steatosis will be difficult to differentiate without histology. In other aspect, some reports suggest steatosis may be a protestive factor for HBV (34,35,54). We should be aware that the inflammation induces by HBV are mainly before age 40. If HBV replication could be suppressed before age 40, the risk of fibrosis progression and/or HCC could be low. On the other hand, NASH is generally happened in older age with exception of lean NAFLD or MASH. In patients with NAFLD and low HBV replication phase, the outcome may be good and be able to clear HBsAg.

Response：

Thank you for your comments. We revised these statements and focused on the management of CHB patients with NASH. Now we state "*The key point of progression is the inflammation activity. Although it would be difficult to differentiate the cause of inflammation from steatohepatitis in CHB patients, the risk of disease progression would be decreased if HBV replication could be suppressed before age*

40. Therefore, the outcome of CHB patients with NASH could be improved in patients with early-stage NAFLD and low HBV replication phase" in Section 2.1.

Point #4. In the mechanism of interaction between HBV and steatosis, please mention T as the risk allele of rs1010023. Please add rs58542926 as the SNP of TM6SF2 you described. The T allele is a minor allele (7% globally). Therefore, may play a role of steatosis in minority.

Response：

Thank you for your suggestion. We have added these evidences. Now we state: in Section 4: *Among these SNPs, chronic hepatitis B patients with the T allele of rs1010023 were more susceptible to hepatic steatosis. The T allele of rs58542926 in TM6SF2 was associated with altered lipids and hepatic steatosis in CHB patients; this substitution was associated with increased hepatitis B virus DNA. Since T allele was prevalent in a minor part of the population (7% globally), it may play a role of steatosis in minority.*

Reviewer #4:

In the review article entitled "Chronic hepatitis B infection with concomitant hepatic steatosis: current evidence and opinion", the authors outlined the relations between chronic hepatitis B (CHB) and hepatic steatosis and then insisted on the necessity of routine administering of concomitant NAFLD lifestyle management and disease screening to ensure better prognoses. While the findings of this study are of interest in a part, the current study is lacking the cutting edge to be accepted for publication. To overcome this limitation, authors are recommended to correct the manuscript according to the comments which are mentioned below. I am afraid to say, but I don't think that the present set of data are reliable enough to draw structural conclusions.

Major comments

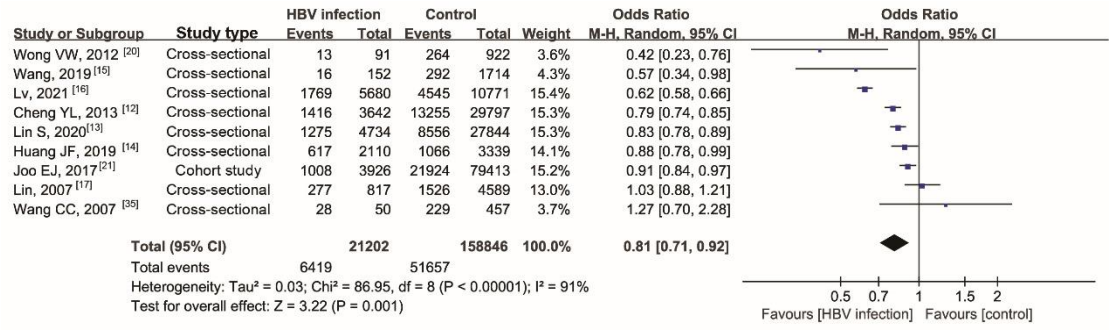
Point #1. Concerning the Fig.1, authors need to show the PRISMA flow diagram showing how the studies included were selected for the meta-analysis. Authors also need to indicate the inclusion and exclusion criteria as well as the methods of data

analysis. Without the information, the basic premise of this research will no longer be valid. In addition, each reference number and type of study design (e.g., retrospective or prospective) should be shown in the Fig.1.

Response: Thank you for your comments. We have made systematic research in the Pubmed-Medline and revised the results of meta-analysis. Now a total of nine studies were enrolled to compare the prevalence of steatosis between CHB patients and normal population in Figure 1. We have added the PRISMA flow diagram as a supplementary file (see *Supplementary Figure 1*. PRISMA (2009) Flow Diagram of Study Inclusion). The search strategy and inclusion/exclusion criteria were added as supplementary file below the manuscript. In addition, we revised the Figure 1 and numbered the references.

Figure legends:

Figure 1. Meta-analysis of the prevalence of hepatic steatosis in HBV infected patients versus control.



Supplementary Figure 1. PRISMA (2009) Flow Diagram of Study Inclusion

Supplementary. Search strategy for Pubmed-Medline

1. "fatty liver"[Title]
2. "steatosis"[Title]
3. "steatohepatitis" [Title]
4. "nonalcoholic" [Title]
5. "FLD" [Title]

6. "NAFLD"[Title]

7. "NASH" [Title]

8. "NAFL" [Title]

9. "intrahepatic lipid" [Title]

10. "hepatic lipid" [Title]

11. "hbv"[Title]

12. "hepatitis b"[Title]

13. "HB virus" [Title]

14. "CHB"[Title]

15. "HBX"[Title]

16. "HBc"[Title]

17. "HBe"[Title]

18. "HBs"[Title]

19. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10

20. #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18

21. #19 AND #20

Inclusion criteria

(a). Cross sectional study or cohort study based on adult population. (b). Reporting data on the prevalence of NAFLD in control / CHB population was available or allowed for calculation. (c). using appropriate methods to diagnose NAFLD.

Exclusion criteria

(a). Patients concomitant with other chronic liver diseases. (b). Duplicates: for studies published in more than one paper, the one reporting the newest data or largest sample size will be considered.