This interesting article conducted by research group of Pisit Tangkijvanich et al. examines the potential role of NTCP polymorphisms (rs2296651 and rs4646287) in nature course HBV infection as well as the progression of liver disease in a large cohort of HBV patients (n=816) and healthy controls (n=205). The authors found that rs2296651 polymorphism was associated with a decreased risk of susceptibility to HBV infection and the development of HCC. The article is easy to read and represent results. However, I do have some concerns as below

Major points:

The authors need to clarify the definition of spontaneous HBV clearance and to distinguish between this term and occult HBV infection. As the authors stated that HBV DNA (table 1) was not performed in spontaneous HBV clearance subjects, it is hard to distinguish between two categories.

Did CHB patients receive antiviral therapy? several factors that contribute to the development of HCC in chronic hepatitis patients. Was HDV infection checked? Because HDV infection is an important factor in this context.

How many CHB cases exhibit liver cirrhosis (LC)? It is interesting to see the role of NTCP SNPs in development of advanced liver disease by examining the distribution of the genotype/allele frequencies between subgroups of chronic hepatitis B patients including CHB, LC and HCC patients.

Were HCC patients in this study cohort performed histological modality (biopsy) to confirm the final diagnosis? The authors need to characterize the clinical features of patients with HCC such as HCC staging (BCLC), treatment etc…
The author stated that "Survival analysis was determined by using the Kaplan-Meier method and compared with the log-rank test." But in this manuscript, I could not see the corresponding results generated from this kind of analysis please correct.

This study tried to evaluate the association between NTCP polymorphism and progression of HBV infection, some concern arise, especially regarding subgroup analysis and multiple tests. Adjusted p values for multiple comparisons should be considered to be calculated and interpreted.

In this study, the authors found that in HCC patients (but not in non-HCC patient), the rs2296651 GG (or CC) genotype had significantly increased rate of HBV replication indicated by HBeAg positivity and HBV DNA levels in HCC patients compared to non-GG genotypes. The authors should discuss this point in the discussion section. Did authors analyse the correlation between rs2296651 genotypes with any other liver function parameters (ALT, AST, bilirubin, Albumin, AFP)? Among 305 HCC cases, how many antiviral treatment naive cases were included in this study?

Minor points:

In introduction section: line 53, 54. Please clarify in details which mutations mentioned?

Title of figure 1 should be changed

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I recommend additional statistical review
Quality of written English
Please indicate the quality of language in the manuscript:

Acceptable

Declaration of competing interests
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal