To The Editor, ***World Journal of Gastroenterology***
Response to Reviewers' comments.
We thank the editors and the reviewers for their comments and provide our responses below. Where necessary, we made changes to the manuscript according to the remarks.

Reviewer #1:
Scientific Quality: Grade B (Very good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Major revision
Specific Comments to Authors: The authors of the Case Control Study "Previous hepatitis B viral infection – underestimated cause of pancreatic cancer" have done a good job in assessing the implication of HBV infection and detecting the presence of HBV-DNA (cccDNA) and viral antigens in pancreatic tumor tissue. Some specific comments to authors include: The original findings of this manuscript are of great importance due to the paucity of studies identifying the presence of HBV markers in PDAC tumor tissue; still, in Table 3, there is reported Patient no 3, who has a peculiar configuration of HBV markers, a detailed discussion about the absence of both pgRNA-HBV and cccDNA, together with the presence of HBV-DNA and HBxAg in the pancreatic tissue can be helpful.

Authors' response:
Thank you for positive feedback and thoughtful comments.
Actually, in the subject 3, pgRNA HBV and cccDNA were not detected despite a significant amount of HBV DNA in the pancreatic tissue. While no HBV replication in this patient was found, integrated HBV DNA could evidently cause the expression of HBx, similar to hepatocellular cancer [Kew MC. Hepatitis B virus x protein in the pathogenesis of hepatitis B virus-induced hepatocellular carcinoma. J Gastroenterol Hepatol. 2011; 26 Suppl 1: 144-152. [PMID: 21199526DOI: 10.1111/j.1440-1746.2010.06546.x].
We discussed this matter in the appropriate section of the manuscript: «*This may mean that in the other two patients, expression of HBx was caused by the integration of the virus into the genome of pancreatic cells. These fragments of viral DNA, which preserve the open reading frame and express HBx, may serve as a basis for cancerogenesis in subjects with pancreatic ductal adenocarcinoma*».

I think that some comments on the studies that did not report a positive association between HBV infection and PDAC, in large study groups after adjustment for age, sex, diabetes and smoking, can be provided by the authors (Chang MC, et al. Hepatitis B and C viruses are not risks for pancreatic adenocarcinoma. World J Gastroenterol. 2014;20(17):5060-5065. doi:10.3748/wjg.v20.i17.5060) Some questions can be consequently raised: What are the similarities and the differences between the studies? Did the authors adjust diabetes as a risk factor? What is the incidence rate of pancreatic cancer in patients from their region? The limitation of the study, as the authors had already concluded, is the small number of the patients and samples of tumor tissues, that can decrease the statistical significance; if the number of study patients cannot be increased, the results remain an issue. I would also recommend the carefully correction for minor typos in the manuscript.

Authors' response:
Actually, the approaches used in the mentioned work and in our study differed. We did not perform multivariate statistics in the present work. This idea is interesting, but it would require sufficient statistical power, significant number of observations and appropriate funding. Our work is exploratory and pilot by nature. Moreover, we studied association of PDAC with not *current* HBV infection, but *previous* (which is more widespread, but not considered dangerous, and therefore more likely evades the attention of healthcare practitioners). The study allowed us to confirm epidemiological relationship between these two conditions, taking into the account about 3-fold higher odds of pancreatic cancer in anti-HBc-positive persons. We hope that publication of our data would serve as a first step, raise interest to the problem and allow us to continue our research.
We enrolled subjects in non-endemic region for HBV infection, where the prevalence of chronic hepatitis B constitutes 4.4 cases per 100 thousand people [Global progress report on HIV, viral hepatitis and sexually transmitted Infections. WHO, 2021 (https://www.who.int/publications/i/item/9789240027077); https://www.rospotrebnadzor.ru/upload/iblock/5fa/gd-seb_02.06-_s-podpisyu_.pdf]. Prevalence of *previous* HBV infection in our country is unknown. According to our results, among healthy volunteers it may be about 13 percent.
On the same time, pancreatic cancer is the ninth most common cancer type in our country, but is on the 5th place among all-cancer mortality here [The Global Cancer Observatory, 2020 (https://gco.iarc.fr/today/data/factsheets/populations/643-russian-federation-fact-sheets.pdf)]
According to your suggestion, we added the reference to the mentioned work in the Introduction.
We revised the manuscript and corrected typos.

Reviewer #2:
Scientific Quality: Grade B (Very good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Minor revision
Specific Comments to Authors: This is a very interesting study with new ideas to find the association between previous HBV infection and pancreatic ductal adenocarcinoma (PDAC). 1. However, the author should mention factors such as NAFLD and diabetes.

Authors' response:
We are grateful to the reviewer for the favorable comments.
Metabolic disorders are known risk factors for pancreatic cancer. We mentioned this in the Introduction section. In the present study we performed univariate analysis to establish association of pancreatic cancer and previous HBV infection.

2. In the PDAC group, with AntiHBc(+) patients, there were 2 cases detected HBVDNA/serum, and 6 cases detected HBVDNA in pancreatic tissue. Why were there total 9 cases instead of 8 cases in Table 3?

Authors' response:
Thank you for bringing this up.

Actually, in table 3, in addition to the data of 8 patients with positive test results for HBV nucleic acids in blood and / or pancreatic tissue samples, we provided the results of special examination of patient No 5. This subject had negative results for these studies and also negative test for HBx protein. At the same time, he had signs of previous HBV infection (anti-HBc-positive confirmed by repeated examination). We suppose that it is correct and important to present these results.
This combination of viral markers may represent the data obtained in the certain timepoint and cannot be easily explained. Unfortunately, it is not possible to repeat special examination of new samples of the pancreatic cancer tissue of this patient later. Future studies of similar cases would help to explain this phenomenon.

3. Why weren't pg RNA HBV and HBxAg performed for all 8 patients who were detected HBV DNA?

Authors' response:
These tests were performed when tissue samples of sufficient quality and size where available, and when the patients gave their written informed consent to perform these tests (separate informed consent is required according to the local law). Due to the mentioned reasons, it was not possible to perform additional studies to all the participants. We revised the description of study procedures to explain better the approaches used in our study.

4. The research sample needed to be larger to be more convincing.

Authors' response:
Thank you for this comment. We share this opinion and mentioned this in the limitation section of the manuscript.

Reviewer #3:
Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Major revision
Specific Comments to Authors: Summary These investigators studied HBV genome and protein in 60 HBsAg negative patients with PDAC and 70 sex- and age-matched controls. They found that anti-HBc seropositive subjects were significantly higher in the case than in the control group. In addition, HBV genomes and HBx protein can be found in tumor tissues of the case group. They suggest that previous HBV infection may contribute to pancreatic carcinogenesis. Comments 1. PBI is not a common abbreviation. Please spell it out initially and replace it with anti-HBc-positive subjects or HBc-negative subject on subsequent text of abstract.

Authors' response:
Thank you for pointing this out. We explained the abbreviation at first mention in the abstract and in the text of the manuscript.

2. In the exclusion criteria section, please indicate how many HBsAg carriers were excluded from the case group.

Authors' response:
Data on the number of patients not included in the study due to the detection of HBsAg are added to figure 1 «Study design and patients' allocation chart».

3. In the Figure 1, please indicate when cases and controls were matched for age and sex.

Authors' response:
The required changes were made to Figure 1.

4. From Table 3, it looks like that not all patients were examined for HBV pregenomic RNA, cccDNA, and HbxAg. Please describe how many and how these patients were selected for each study in the study procedure section.

Authors' response:
Thank you for bringing this up. We revised the description of study procedures. In the revised version it reads as follows:
«*All 18 anti-HBc-positive patients with PDAC were examined for HBV DNA in the pancreatic tumor tissue. In 8 of them, the quality and the size of the tissue samples was suitable for additional testing for HBV pregenomic RNA and cccDNA. Five patients had suitable samples and gave additional consent for immunohistochemistry analysis (required by the local law)*»

5. In legend of Figure 2, please clarify the study samples were tumor or non-tumor part in case group. Please also describe how the control pancreas tissue was obtained.

Authors' response:
We made appropriate corrections to the figure legend and the "Collection of samples" section.

6. In the result section, table 1 seems to be a description of Table 2.
Authors' response:
We apologize for this mistake. It was corrected in the revised version of the manuscript.

7. In Table 2. Please remove Black race line. The HBV DNA in blood and pancreas should be separated in the two lines. Please indicate nil in the control pancreas HBV DNA. The percentage should be according to the number of anti-HBc-positive cases.

Authors' response:
Table 2 has been amended and revised.

8. The first sentence of the discussion is not appropriate. Present of the HBV genome in cells does not indicate a direct relation to carcinogenesis. For example, HBV genomes are presented in hepatocytes, but not all of them developed HCC.

Authors' response:
Thank you for your suggestion. We rephrased this sentence according to the mentioned above.

9. PC is the third leading cause of cancer-related deaths in the US, and fourth in the EU. These regions are not high HBV infection areas. On the other hand, those HBV endemic areas, such as Africa and East Asia, show relatively low pancreas cancer related death. This contrasts with previous HBV infection increase risk for pancreas carcinogenesis. Please discuss this discrepancy in the discussion.

Authors' response:

Thank you for this thoughtful comment. It is difficult to draw absolute parallels in this case. There are multiple risk factors for pancreatic cancer, while HBV infection could be only one of them. The epidemiology of previous HBV infection is not sufficiently studied. In contrast, the prevalence of current HBV infection may be associated with higher rates of mortality from other cancers (for example, HCC-related). Moreover, the influence of other factors (not similar in different regions) should be taken into the account (*i.e.*, rates of alcohol consumption, processed meat intake, smoking, obesity, *etc.*). Standards of living and life expectancy may also be the factors that influence statistics on PC.