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

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: This is an interesting case report to reveal that HBsAg-negative patients with pancreatic ductal adenocarcinoma, in whom the markers of HBV were detected in blood and in the tumor tissue. This reflects potential involvement of the virus in the etiology and pathogenesis of pancreatic ductal adenocarcinoma. 1, All images are highly professional, however I suggest the authors can guide the readers to the meaning of the images appropriately; otherwise, it is likely to cause misunderstandings. 2, Sufficient quality and quantity for Fig1, therefore, the author need perform statistically analyse for these fig. 3, The figure legend requires further revise, and manuscript also needs English proofreading.

Authors' response: We are grateful to the reviewer for the favorable comments and thoughtful approach to described cases. According to the comments, we transferred the information about Ki67 index to the figure's legend and added information about count of HBx - positive cells in pancreatic tissue to table1. Professional linguist proofread the manuscript before revised version was submitted.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: Morozov et al. described two patients with pancreatic ductal adenocarcinoma (PDAC) who were serologically HBsAg negative but antiHBcAb positive. pgRNA and cccDNA were detected in PDAC of subject 1 by RT-PCR and PCR, respectively, and HBxAg was immunohistochemically detected in PDAC of both patients. Thus, they suggested association between HBV infection and PDAC.

This is an interesting study that may provide a new perspective on the development of PDAC. I have some comments to improve the manuscript. Major points: 1. (Figure 1) If HBxAg is associated with PDAC carcinogenesis, it should be expressed in all PDAC cells. However, HBxAg is expressed only in a subset of PDAC cells in cases 1 and 2. Please explain the reason.

Authors' response: Thank you for your comments. According to the literature, the mean number of HBx-expressing cells in HBs-negative, HBV DNA-positive patients with hepatocellular carcinoma is about 30% of the tumor tissue and 20% of the rest of hepatocytes [**Poussin K**, Dienes H, Sirma H, Urban S, Beaugrand M, Franco D, Schirmacher P, Bréchot C, Paterlini Bréchot P. Expression of mutated hepatitis B virus X genes in human hepatocellular carcinomas. Int J Cancer. 1999 Feb 9;80(4):497-505. doi: 10.1002/(sici)1097-0215(19990209)80:4<497::aid-ijc3>3.0.co;2-8. PMID: 9935147.]. The rate of HBx-expressing cells in pancreatic cancer has not been reported yet. In pancreatic adenocarcinoma, HBx may be expressed from HBV DNA fragments integrated into the human genome and reveal more active pro-oncogenic properties. It may be indirectly supported by high values of Ki-67 proliferative index (> 50%) in the described cases, which commonly found only in the minority of cases of pancreatic ductal adenocarcinoma (~12%) [**Kim H**, Park CY, Lee JH, Kim JC, Cho CK, Kim HJ. Ki-67 and p53 expression as a predictive marker for early postoperative recurrence in pancreatic head cancer. Ann Surg Treat Res. 2015;88(4):200-207. doi:10.4174/astr.2015.88.4.200; **Pergolini I**, Crippa S, Pagnanelli M, et al. Prognostic impact of Ki-67 proliferative index in resectable pancreatic ductal adenocarcinoma. BJS Open. 2019;3(5):646-655. Published 2019 May 10. doi:10.1002/bjs5.50175].

2. (Figure 1) Ki-67 index looks like nearly 100% in Control and may be misleading. Choice of figures had better be reconsidered.

Authors' response: Thank you for your comment. The field of visions within the same samples were amended.

Minor points: 3. (p.3, l.16) pT1G2R0N0LVI0 PNI0 in case 1, pT2N0V0Pn1R0TRS3 in case 2: The source of TNM staging, for example UICC or AJCC, should be stated and cited. PNI and Pn1 should be unified and TRS should be spelled out or explained. 4. (p.7, l.26)

pT1G2R0N0 LVI0 PNI0: Please refer to 3. 5. (p.8, l.9) pT2N0V0Pn1R0 TRS3: Please refer to 3.

Authors' response: Thank you for this valuable comments. We used UICC staging system. According to the comments, the staging were updated and referenced appropriately. The Modified Ryan Scheme for **Tumor Regression Score** was recommended for routine use by the College of American Pathologists [**Amin MB**, Edge SB, Greene FL, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York, NY: Springer; 2017]

6. (p.3, l.11) Beside standards of care: Besides standards of care 7. (p.6, ll.25-28) ℃ is garbled. 8. (p.7, l.15) LAS X Leica: LAS X (Leica 9. (p.7, l.4) 4% solution of formaldehyde: Isn't this paraformaldehyde? 10. (p.9, l.3) there are only two studies described HBx expression: there are only two studies that described HBx expression

Authors' response: these misprints were corrected, thank you.

11. (p.9, l.24)seems reasonable: Judging from the context, isn't this "seems unreasonable" or "may not be reasonable?"

Authors' response: the context is checked and correct.

Please check. 12. (Table 1) "cccDNA, copies/cell x 10-6" and "Ki-67 index, median (%)": These had better be followed by (pancreatic tissue), too.

Authors' response: we added "pancreatic tissue" and amended the table (values of Ki-67 index are transferred to the figure's legend).

(1) Science editor:

Authors showed two cases with PDAC. Authors suggested that HBV integration might be found in PDAC cells. This is interesting findings, but the conclusion was unclear from the data shown in the manuscript. HBx protein was found only in limited cells with Ki-67 positive. But past HBV infection before PDAC development was suggested in present cases. The reason of HBx protein localization was unclear. In case 2, more

HBV-DNA was found than in case 1. But cccDNA or pgRNA were not found. Contamination or false-positive could not be ruled out. The results of PCR should be shown with negative and positive control. Full-sequence data might be helpful.

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Transfer to another BPG Journal

Authors' response: The risk of contamination is negligible, as HBV DNA was not detected in blood. We added supplementary figure 1 according to the comment of Science editor.