Dear editor and reviewers,

Thank you for the invitation to revise our manuscript (Manuscript NO:77733), which we have modified extensively according to the reviewer comments. The changes are highlighted with red font and yellow background, and we also submitted a clean version. Below we reply point-by-point to those comments. However, because the revised draft submission system could not upload these two files, I sent them as attachments through email.

Thank you again for the opportunity to revise our manuscript, and we hope the new version can be considered suitable for publication.

Sincerely yours,

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RESPONSES TO COMMENTS FROM REVIEWER

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: Authors have evaluated the expression and clinical

significance of VCAN in relation to HBV related cirrhosis in comparison to HCC. I have certain issues. 1. The authors have included only HBV related cirrhosis and HCC. On the other hand, the title of the article reflects its generalizability for HCC. In my opinion, Title should include HBV as etiology of HCC.

Author: Thanks for your helpful comments and suggests. We have revised the title to: VCAN highly expresses in hepatocellular carcinoma caused by HBV and is a potential biomarker for immune checkpoint inhibitors.

2. The study has been conducted in China, wider evaluation of VCAN expression is essential in other geographical regions including diverse ethnic population.

Author: Thanks for your suggest. In this study, we have preliminatively evaluated the expression of VCAN RNA expression in TCGA(Figure 1) and ICGC(Figure S1), in which TCGA covers patients with liver cancer caused by different etiology in various regions of the world, and ICGC-LIRI-JP covers patients with liver cancer in Japan caused by HBV or HCV, while ICGC-LICA-FR is from France and most of the causes are alcohol or high fat. If we have the opportunity later, we will test VCAN expression levels in patients with liver cancer of other causes or other regions or ethnicities.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors:

1. **This article analyzed the role of VCAN in HCC related with HBV and thought that high VCAN could be a possible biomarker of the poor prognosis of HCC, and its' role of immunomodulatory mechanism in HCC deserves attention. This new hypothesis has certain clinical practice guidance.**

Author: Thanks for your comments. We would expand the sample size to further verify the possibility of VCAN as a diagnostic marker for HBV-associated liver cancer and as a predictive marker for the efficacy of immune checkpoint inhibitors in liver cancer treatment. We hope that these results will provide guidance for clinical practice.

2. **If the references and hypothesis are further validated by expanding the number of cases, liver tissue specimens, and relevant oncology and immunological indicators, the quality of the study will be further improved.**

   Author: Thanks for your helpful results. We have collected a small sample size of HBV associated liver cancer tissue samples from different sources in this paper, detected the RNA expression level of VCAN in liver cancer tissue, and found that VCAN was highly expressed in liver cancer tissue. We will expand the sample size to continue to detect the expression level of VCAN in liver cancer tissue and serum of liver cancer patients, as well as CD44, CD200, PD1, CDLA4 and other immune checkpoint levels.