Responding to reviewer comments

Reviewer 1

Comment No.1: There are too many diagrams in the paper. Therefore, it is suggested to put the non-main chart into the supplementary material.
Answer: We strongly agree with the reviewer's comment. In the text, we deleted the correlation scatter plots in Figure 5 and 7. Add these deleted images to the supplementary material(Figuer S1 and Figure S2).

Comment No.2: The words “the results” are mentioned several times in the article, and it is suggested to correct to “the result”.
Answer: Thank you very much for the reviewer's comment. We are sorry for the mistake in our details. We have changed all the words“the results” to “the result” according to your suggestion.

Comment No.3: There are many grammatical errors in the article. It is suggested to ask professional English speakers to polish the language.
Answer: We attach great importance to this reviewer 's comment, and we have submitted the final manuscript to a professional language service company for revision and polishing, and the language editing certificate has been uploaded to the attachment.

Comment No.4: The process of meta-analysis is not reflected, so it is suggested to add content to the part of methods.
Answer: Reviewers' comments aroused great concern. We decomposed and refined the methodology of meta-analysis, and decomposed the previous 2.13 into two parts: 2.13 and 2.14, making the content and structure of meta-analysis more complete.

Reviewer 2

Comment No.1: The Authors showed that the expression of BCYRN1 was higher in HCC tissue compared to healthy liver. The HCC developed, in the 90% of cases, on cirrhotic liver and it is often the evolution of preneoplastic lesions. So, was analyzed the expression of BCYRN1 in the peritumoral tissue (cirrhotic liver)? I think that it could be a useful information to establish if BCYRN1 expression increase in cirrhotic tissue compared to controls and could be used as diagnostic marker. Please explain if it is possible to extrapolate this information from the database.
Answer: The reviewer put forward valuable opinions, which caused us to think deeply. In HCC cases, HCC is mostly developed from cirrhosis, especially in China, where the incidence of hepatitis B is relatively high. TCGA (The cancer genome atlas) was developed by the National Cancer Institute(NCI) and the National Human Genome Research Institute(NHGRI) at The joint project, launched in 2006, contains clinical data on various human cancers (including subtypes of tumors), genomic variation, mRNA expression, miRNA expression, methylation and other data, which is an important source of data for cancer researchers. The specimens included in TCGA are divided into two types, one is normal tissue and the other is cancer tissue. Normal tissues were generally paracancer tissues of patients, and unhealthy paracancer tissues of some patients were excluded. Therefore, 374 cases of HCC tissues were included, while only 50 cases of normal paracancer tissues were included. We hypothesized that most of the remaining paracancer tissue

was cirrhosis, so it was eliminated. We were unable to use the TCGA database to explore whether BCYRN1 was abnormally expressed in cirrhosis. However, the reviewer 's idea is invaluable, and we could collect cirrhotic specimens and examine BCYRN1 expression to determine whether it could serve as a biomarker for cirrhosis. It provides a new direction for our scientific research. Thank you to the reviewer for valuable comments.

Comment No.2: The Authors concluded that BCYRN1 expression was correlated with histological grade, but in the figure 3C seems the expression increased in G2 and G3 stages, but returns to lower levels in G4 stage, not significantly different from the G1 stage. How the Authors explain this result? I think that should be better discussed in the text.
Answer: We attach great importance to the comments of reviewer. According to our findings and reasoning, the worse the pathological grade, the stronger the proliferative and invasive of HCC, and the higher the expression level of BCYRN1 should be. However, the expression of stage G4 in Figure 3C is low, which is not in line with our expected results. We deeply explored the reasons behind it. As can be seen from the downloaded clinical data, there were 54 patients in GI stage, 179 patients in G2 stage, and 123 patients in G3 stage, while there were only 13 patients in G4 stage. Therefore, the number of patients in G4 stage was significantly lower than those in other stages, and the sample size was too small to be representative. Given sufficient sample size, the results are estimated to be in line with our expectations. We added this section to the discussion in the article, marked in red.

Comment No.3: The high expression of BCYRN1 seems to be associated with a poor prognosis, but the chemosensitivity of HCC seems higher in the group with BCYRN1 expression. This result seems to be countersense. How the Authors explain it?
Answer: The reviewer 's comments aroused our great concern. From Figure 9A, we can conclude that the HCC drug chemosensitivity was higher and the therapeutic effect was better in the high BCYRN1 expression group. However, there is no direct correlation between the level of drug sensitivity and the prognosis of patients. For example, in lung cancer, small cell lung cancer has the highest sensitivity to chemotherapeutic drugs and the best therapeutic effect, but its prognosis is the worst, because small cell lung cancer soon appears drug resistance after chemotherapy, leading to tumor recurrence and metastasis. Therefore, high expression of BCYRN1 has a poor prognosis, but chemosensitivity is high and chemotherapy is still recommended.

Reply to the editor

Comment No.1: The quality of the English language of the manuscript does not meet the requirements of the journal. Before final acceptance, the author(s) must provide the English Language Certificate issued by a professional English language editing company.
Answer: We attach great importance to the editor 's comment, and we have submitted the final manuscript to a professional language service company for revision and polishing, and the language editing certificate has been uploaded to the attachment.

Comment No.2: Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the

Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author,“Impact Index Per Article” under “Ranked by” should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at(https://www.referencecitationanalysis.com/).

Answer: We are grateful to the editors for their valuable input. Through our understanding, RCA is indeed an extremely valuable citation tool. We have found and cited two valuable literature related to BCYRN1 through the RCA tool, 17 and 29. We also added our thanks to it in the acknowledgements section.

Comment No.3: The reviewer and editor would like to see the addition of independent cohort validation and associated experimental studies in the revision.

Answer: Our research becomes more convincing when supplemented by experimental research. However, we lack the laboratory conditions to complete the project in a short period of time, which is also mentioned in the discussion section. However, our study was finally verified by meta-analysis. All the original studies included in the meta-analysis were high-quality experimental studies that detected the expression of BCYRN1 in HCC samples by PCR and then analyzed the prognosis of patients. Finally, the same conclusion as bioinformatics is obtained, which effectively verifies the analysis results of the database.