Reviewer #1:

Major points

1. **Response to comment:** (*Unfortunately, the image results of the article were not viewed for download in the review system.*)

Response: Thank you for your comments. We have uploaded all image results as required by the journal.

2. Response to comment: (*What is the significance of choosing the GSE140228 data uploaded in 2019, and why was it not statistically analyzed by combining multiple existing data? Is the amount of data used to train and validate the model sufficient to support the conclusions drawn? It is recommended that more data be utilized for analysis.*)

Response: Thank you for your constructive comments. Due to severe batch effects across different sources of single-cell data, significant biological variations in single-cell RNA-seq datasets from various studies are often influenced by these data source discrepancies [PMID: 29121214]. This limitation hinders our ability to conduct research across multiple single-cell datasets. Additionally, not all single-cell datasets have a rich diversity of cell types or sufficient cell numbers, and poorly quality-controlled datasets may not perform as well as a high-quality dataset. Therefore, we selected the GSE140228 dataset for our study, which contains the largest number of cells, 62,530 in total and includes almost all immune cell types.

In fact, we have included as much HCC data as possible in our study. We obtained transcriptomic data from the TCGA-LIHC dataset, which includes 375 HCC samples and 50 paired adjacent normal tissues. Among these, 365 patients had complete survival data, clinical pathological information, and somatic mutation data. Additionally, we gathered transcriptomic and survival data from 232 HCC patients in the ICGC database. Furthermore, transcriptomic and survival data from 115 HCC patients were retrieved from the GSE76427 dataset. The volume of data used for training and validation in our study surpasses that of most recent HCC research [PMID: 39100078][PMID:

39085893], and our model has demonstrated strong performance across multiple datasets. Therefore, we believe that the amount of data used for training and validation strongly supports the conclusions we have drawn.

3. Response to comment: (*The article specifies that riskscore is the only independent prognostic factor for HCC. Would the AUC value be higher if risk factors, age, gender, grading, and staging were jointly referenced as prognostic factors, and would this be a more accurate assessment?*)

Response: Thank you again for your constructive comments. We have confirmed that the risk score is the only independent prognostic factor for HCC (Figure 6A-B). The risk score is highly correlated with HCC stage, grade, and T stage, indicating that it can replace these traditional clinical and pathological factors without adding unnecessary complexity to the model (Figure 6D-E). Including other clinical and pathological factors without independent prognostic value is illogical. On the other hand, other clinical and pathological factors have a poor predictive ability for HCC prognosis, and the diagnostic capability of the risk score far exceeds that of these factors (Figure 6C). Incorporating such less predictive prognostic factors would significantly compromise the overall AUC value and contradict the logical framework of the analysis.

4. Response to comment: (*There is duplication in the titles BRGs prognostic model and TCGA official immune typing and BRGs prognostic model evaluates immunotherapy efficacy.*)

Response: Thank you for your constructive comments. We have merged the duplicates.

5. Response to comment: (*Is it sufficiently accurate to classify HCC patients into three subtypes using only the 11 BRGs in the prognostic model? Have the corresponding typing preferences been validated in the clinic?*)

Response: Thank you for your constructive comments. Based on Delta area and CDF curves, we observed good stability in sample clustering when k=3 (Figure 9A-B). The consistency matrix heatmap exhibited a relatively consistent blue shading when k=3 (Figure 9D). PCA and tSNE analyses effectively differentiated HCC patients according to the novel molecular subtyping (Figure 9G-H). These findings collectively indicate that the classification of HCC patients into three subtypes is accurate and successfully distills the heterogeneity among HCC patients. Due to the difficulty in obtaining large-scale HCC clinical sample sequencing data and the challenge of ensuring its quality, our ability to validate with new clinical samples is currently limited. We have included a discussion of the limitations on this point in the Discussion section.We are committed to addressing this in the future. It is worth noting that our conclusions have already been validated using large-scale data from various databases such as TCGA, ICGC, and GEO, which further confirms the validity and reproducibility of our findings.

6. Response to comment: (*The results of the immune microenvironment and cellular infiltration support the cooperation between B cells and T cells in the suppression of HCC, please elaborate in the discussion the proof that B cells have more value than T cells in HCC treatment.*)

Response: Thank you for your constructive comments. We have added a discussion on this topic. Similar to regulatory T cells (Treg), B cells can also exhibit regulatory phenotypes to suppress immune responses. They express inhibitory receptors on their surface, akin to immune checkpoint genes. These include a variety of immune checkpoint molecules like PD-1 and its ligands PD-L1/L2, which play diverse regulatory roles in both humoral and cellular immunity (PMID: 38391970). Recent findings in hepatocellular carcinoma (HCC) reveal that B cells with elevated PD-1 expression, when encountering PD-L1-expressing cells, induce T cell suppression by releasing IL-10. Blocking PD-1 on B cells with checkpoint blockade antibodies has shown promise in enhancing cancer immunotherapy (PMID: 29144460). Anti-PD1

therapy has become the preferred immunotherapy for treating HCC. However, anti-PD1 therapy targeting T cells has only achieved a 15% response rate in HCC patients (PMID: 32402160). In this context, anti-PD1 therapy targeting B cells may potentially become an important approach to improving the efficacy of immunotherapy for HCC patients.

Reviewer #2:

Major points

1. **Response to comment:** (*Your research on "B cell-specific signatures reveal novel immunophenotyping and therapeutic targets for hepatocellular carcinoma" presents an interesting and valuable exploration into the role of B cells in hepatocellular carcinoma (HCC). The team's expertise in various medical disciplines, including hepatobiliary and pancreatic surgery, pharmacy, basic medical sciences, and gastrointestinal surgery, provides a strong multidisciplinary foundation for this study. The breadth of your institutional affiliations, ranging from Zhongnan Hospital of Wuhan University, Union Hospital at Tongji Medical College, Nanjing Medical University, The Second Affiliated Hospital of Kunming Medical University, and the Second People's Hospital of Jiaozuo City, suggests a collaborative effort that leverages diverse resources and perspectives. This integrated approach is essential for gaining a comprehensive understanding of the complex interplay between B cells and HCC.*)

Response: Thank you for your kind words. We are truly honored to receive recognition from a professional reviewer like yourself.

We hope the revised manuscript could address all the reviewer’s concerns .