3 SCIENTIFIC QUALITY

Reviewer #1:
Scientific Quality: Grade B (Very good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Minor revision
Specific Comments to Authors: In this study, the authors aimed to establishing a prognostic survival model with 7 prognostic genes able to predict overall survival in patients of hepatocellular carcinoma (HCC) and revealing the immune profile of tumor microenvironment (TME). They extracted data from TCGA and ICGC datasets for screening prognostic genes along with developing and validating a 7-gene prognostic survival model by method of weighted gene co-expression network analysis (WGCNA) and LASSO with cox regression. They found 7 prognostic genes for signature construction. Survival receiver operating characteristic (ROC) analysis demonstrated the good performance of survival prediction. TBM could be considered as an independent factor in HCC survival prediction. Of interest, several immune checkpoints including VTCN1 and TNFSF9 were found to be associated with the 7 genes and risk scores. Different combinations of checkpoint blockade targeting inhibitory CTLA4 and PD1 receptors, and potential chemotherapy drug held great promise for specific HCC therapy. The authors concluded that their novel 7 genes (CYTH3, ENG, HTRA3, PDZD4, SAMD14, PGF, PLN) prognostic model shows high predictive efficiency thus supporting the TBM analysis based on the 7 genes as a predictive marker of the immune response in HCC for clinical application The study is of interest, however, in my opinion, the authors should tried to focus their research on the topic now of major clinical impact. Genetic studies exploring and searching for genetic influences in HCC development as well as treatment response/resistance, have been extensively studied. However, with the recent increasing development of systemic treatments, the authors should discuss the recent evidence supporting the higher anti-tumor efficacy of combination treatment strategy based on the combination of tyrosine kinase inhibitor plus immune checkpoint inhibitors as well-described in a recent comprehensive review addressing the improved efficacy and overall survival and safety profile of combination (TKI plus ICI) treatments, as recently reported (TKIs in combination with immunotherapy for hepatocellular carcinoma. Expert Rev Anticancer Ther. 2023 Mar;23(3):279-291). -To improve the clinical significance I would suggest to recall and discuss the following 2 topics both related to the genetic impact in HCC development and immune cells pattern: 1) recent studies suggested a genetic role in hepatocarcinogenesis according to the underlying liver disease which are now changing in the changing scenarion of HCC as recently demonstrated in a largen cohort of HCC patients (The changing scenario of hepatocellular carcinoma in Italy: an update. Liver Int. 2021 Mar;41(3):585-597.). This important epidemiological issue should be recalled and discussed. 2) one of the most abundant immunosuppressive cell population in the tumor microenvironment is

the CD4+ CD25+ FOXP3 T cell population which also amply express CTLA4 and PD1 thus representing a direct target of ICIs, as recently described in a comprehensive review addressing the role of Tregs according to etiology of underlying liver diseases (Hepatocellular carcinoma in viral and autoimmune liver diseases: Role of CD4+ CD25+ Foxp3+ regulatory T cells in the immune microenvironment. World J Gastroenterol. 2021 Jun 14;27(22):2994-3009.). 3) the last point worth mentioning is the impact of immune cell profile also in the treatment reponse to locoregional treatments such as transarterial chemoembolization (TACE). It has been demonstrated that CT-radiomics signature could effectively predict the prognosis and treatment response of HCC, which is also associated with the tumor microenvironment heterogeneity (A radiomics signature associated with underlying gene expression pattern for the prediction of prognosis and treatment response in hepatocellular carcinoma. Eur J Radiol. 2023 Oct;167:111086.). On the contrary, the authors should recall and discuss that previous suggested prognostic score such as the ART score are not able to predict the outcomes of HCC patients who underwent TACE as previously demonstrated (The ART score is not effective to select patients for transarterial chemoembolization retreatment in an Italian series. Dig Dis. 2014;32(6):711-6.).

Response: Thank you for your revision. To improve the clinical significance, I had added the relevant content in the manuscript of Discussion part, which were highlighted the revised/added contents with yellow color. The specific context is written below:

In recent studies, immune checkpoint inhibitors (ICIs) plus tyrosine kinase inhibitors (TKIs), which are antiangiogenic drugs, seemed more effective in antitumor therapy, especially in reversing the immunosuppressive profile of the TME and improving the efficacy, OS and safety profile(31). We must be more cautious and precise in the utilization of ICIs for HCC treatment, given the escalating incidence of HCC cases attributed to "metabolic" and "metabolic+alcohol" etiologies, as well as the intricate interplay between liver metabolism and immune system regulation (32, 33). In addition, Tregs are the most prevalent suppressor cells in the TME and express immune checkpoints such as PD-1 and CTLA-4, showing a potential therapeutic role of targeting Tregs in HCC treatment(34). In our research, we observed an association between Tregs and patients at higher risk, suggesting that PD-1 and CTLA-4 might have the potential to alleviate patients by specifically targeting Tregs. Furthermore, the utilization of transarterial chemoembolization (TACE) has the potential to stimulate the generation of antigen-specific CD4+ and CD8+ T cells in patients with HCC, thus rendering the combination of TACE and ICI treatment highly promising in terms of its application prospects(35). Radiogenomics research associated with TME heterogeneity has also made progress in recent years. Dandan Wang established a CT-derived radiomics signature based on 7 hub genes and revealed infiltration of CD4+ T cells, plasma cells and macrophages among different risk groups(36). It is noteworthy that the Austrian team had devised an ART score for assessing the potential efficacy of repeated TACE treatment in patients, although this score had not yet undergone clinical validation(37). This result implied that additional clinical validation is needed for the exploration of the TME and ICI in our research.

Besides, we had also polished the language with the help from Aje. The certification was uploaded as well.

Reviewer #2:
Scientific Quality: Grade C (Good)
Language Quality: Grade C (A great deal of language polishing)
Conclusion: Major revision
Specific Comments to Authors: -the study is in need of major language editing - the clinical significance is lacking
Response: Thank you for your revision. The language had been polished with the help from AJE. The certification from AJE was uploaded as well. Besides, to improve the clinical significance, we also recall and discuss the changing scenarion of HCC, role of CD4+ CD25+ Foxp3+ regulatory T cells in the immune microenvironment and impact of immune cell profile in the treatment response to locoregional treatments. The added contents were highlighted with yellow color.