

### 3 SCIENTIFIC QUALITY

Please resolve all issues in the manuscript based on the peer review report and make a point-by-point response to each of the issues raised in the peer review report, and **highlighted the revised/added contents with yellow color in the revised manuscript**. Note, authors must resolve all issues in the manuscript that are raised in the peer-review report(s) and provide point-by-point responses to each of the issues raised in the peer-review report(s); these are listed below for your convenience:

Reviewer #1:

**Scientific Quality:** Grade B (Very good)

**Language Quality:** Grade B (Minor language polishing)

**Conclusion:** Minor revision

#### **Specific Comments to Authors:**

This manuscript addresses a clinically relevant issue and presents well-organized research. Authors study the effectiveness of radiofrequency ablation in combination with sorafenib for treating patients suffering from liver cancer with portal hypertension and to analyze the prognostic factors. The methodology is sound, and the results support the efficacy of RFA combined with sorafenib in treating liver cancer with portal hypertension. The inclusion of adverse reactions and survival rates provides a comprehensive view. However, the study's limitation lies in the sample size, and a larger-scale investigation is warranted for robust conclusions. Others, In the Methods section on the page 1, 'the research group received radiofrequency ablation in combination with sorafenib,' repeated twice. The paper is well-written, but a more in-depth discussion on the adverse reactions and potential strategies for mitigation would be beneficial.

1. R: Thanks for your comments. We have added a paragraph to discuss the limitation of the sample size.

Revised paragraph: It is also necessary to acknowledge the limitation of the sample size, which underscores the need for a more comprehensive investigation to establish stronger conclusions. While the present study offers valuable insights, a larger-scale investigation is warranted to reinforce the robustness and generalizability of the findings. Therefore, conducting a study with a larger sample size would address this limitation and ensure a broader applicability of the results, enhancing the overall strength of the conclusions.

2. R: Thanks for your comments. We have removed the repeated sentence.

3.R: Thanks for your comments. We have added in-depth discussion on the adverse reactions and potential strategies for mitigation.

Revised paragraph: The findings of this study contribute to a better understanding of the efficacy and potential challenges associated with the combined therapy of radiofrequency ablation and sorafenib for the treatment of liver cancer complicated by portal hypertension. While the results indicate a promising improvement in patient outcomes, it is essential to acknowledge the observed increase in adverse reactions, particularly in the form of diarrhea, rash, nausea, vomiting, and fatigue within the research group. These adverse reactions have been documented as common side effects of sorafenib therapy. Therefore, in light of these findings, it is imperative to address potential strategies for mitigating these adverse events to ensure the overall well-being and treatment adherence of the patients.

The management of adverse reactions related to sorafenib therapy becomes paramount in ensuring the continued effectiveness of the treatment approach. Given the identified adverse reactions in the research group, it is crucial for healthcare providers to proactively monitor and manage these side effects to optimize patient tolerance and compliance. Strategies for mitigation may

include personalized patient education on potential side effects, proactive symptom management, dose adjustments based on individual tolerability, and prompt intervention for severe adverse events. Additionally, comprehensive supportive care measures, such as nutritional support and psychological counseling, can play a significant role in contributing to the overall well-being of patients undergoing this combined therapeutic approach.

Furthermore, future research endeavors should focus on investigating novel approaches to reduce the incidence and severity of these adverse events, potentially through the exploration of alternative dosing regimens, the use of adjunctive medications for symptom management, or the identification of predictive markers for susceptibility to specific adverse reactions. By addressing these challenges, healthcare providers can work towards optimizing the therapeutic benefits of radiofrequency ablation in combination with sorafenib while minimizing the impact of treatment-associated adverse reactions on patient quality of life.

Reviewer #2:

**Scientific Quality:** Grade B (Very good)

**Language Quality:** Grade B (Minor language polishing)

**Conclusion:** Minor revision

**Specific Comments to Authors:**

The study investigates the effectiveness of RFA in combination with sorafenib for liver cancer patients with portal hypertension, analyzing prognostic factors. One hundred patients were divided into a research group (RFA with sorafenib) and a control group (RFA only). The research group showed significantly higher total efficacy (82.00%) than the control group (56.00%). Liver function, portal vein pressure, and tumor markers improved more in

the research group. Adverse reactions were higher in the research group, with a 3-year survival rate of 72.00%, compared to the control group (40.00%). Multivariate analysis identified high Child-Pugh grade, tumor size (6-10 cm), history of hepatitis, no sorafenib use, liver cancer stage IIIC, and previous splenectomy as poor prognostic factors. The study provides valuable insights into the combined treatment of RFA and sorafenib for liver cancer with portal hypertension. The methodology is robust, with clear inclusion/exclusion criteria and rigorous statistical analyses. The results show promising efficacy, although the increased adverse reactions in the research group are noteworthy. However, the small sample size is a limitation, and a more extensive study is necessary to generalize the findings. Additionally, a detailed discussion on the mechanisms underlying the treatment's efficacy would enhance the paper.

1. R: Thanks for your comments. We have added a paragraph to discuss the limitation of the sample size.

Revised paragraph: It is also necessary to acknowledge the limitation of the sample size, which underscores the need for a more comprehensive investigation to establish stronger conclusions. While the present study offers valuable insights, a larger-scale investigation is warranted to reinforce the robustness and generalizability of the findings. Therefore, conducting a study with a larger sample size would address this limitation and ensure a broader applicability of the results, enhancing the overall strength of the conclusions.

2. R: Thanks for your comments. We have added detailed discussion on the mechanisms underlying the treatment's efficacy.

Revised paragraph: The observed efficacy of the combined therapy involving radiofrequency ablation and sorafenib in the treatment of liver cancer complicated by portal hypertension can be attributed to the synergistic actions of these modalities, each targeting specific aspects of the disease pathophysiology. Radiofrequency ablation, as a local ablation therapy, exerts

its effects by inducing thermal damage to liver tissue, leading to cellular degeneration and irreversible necrosis. This approach is particularly advantageous in cases of unresectable liver cancer complicated by portal hypertension, where surgical intervention may not be feasible due to the patient's clinical condition. The localized tissue destruction achieved through radiofrequency ablation contributes to a reduction in tumor burden, thereby alleviating portal vein pressure and improving liver function, as evidenced by the observed reduction in transaminase levels and portal venous pressure in the study population.

Concurrently, the incorporation of sorafenib, an oral tyrosine kinase inhibitor, complements the effects of radiofrequency ablation by targeting critical molecular pathways involved in neovascularization and tumor progression. Sorafenib's mechanism of action includes the inhibition of vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR), which are known to play pivotal roles in the promotion of tumor angiogenesis and vascular remodeling. By disrupting these signaling pathways, sorafenib not only impedes tumor neovascularization but also exerts modulatory effects on portal hypertension, thereby contributing to the overall improvement in clinical outcomes observed in the study.

Moreover, the synergy between radiofrequency ablation and sorafenib may extend beyond their individual mechanisms of action. It is plausible that the localized tissue injury caused by radiofrequency ablation creates an environment conducive to the anti-tumor effects of sorafenib, potentially enhancing its penetration and efficacy within the tumor microenvironment. This interplay between the two treatment modalities underscores the importance of combination strategies in addressing the complex interplay of factors associated with liver cancer complicating portal hypertension, with the potential to offer a more comprehensive and efficacious approach to disease management.