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PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 120606

Title: Imaging Tumor Heterogeneity to Predict Response to Transarterial Chemoembolization in Hepatocellular Carcinoma

Provenance and peer review: Invited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 08040211
Position: Peer Reviewer
Academic degree and professional title: Associate Professor, MD
Reviewer's Country/Territory: Chile
Author's Country/Territory: United States

Manuscript submission date: 2026-03-02

Reviewer chosen by: Jia-Lin Zhang

Reviewer accepted review: 2026-03-31 00:50

Reviewer performed review: 2026-04-03 01:55

Review time: 3 Days and 1 Hour

Content to be reviewed	Does the research scope comply with ethics? **Yes** Are additional experiments needed for the study? **Yes** Will the manuscript's content be of interest to readers? **Yes** Is the manuscript's text correct, concise, and clear? **Yes** Do authors only cite their own earlier publications? **No** Are all references related to the topic of the manuscript? **Yes** Do authors omit important references? **Yes**

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	Are all references necessary and reasonable? **Yes** Is the Conclusion reasonable? **Yes** Is the content of the Discussion reasonable? **Yes** Are the figures and tables numbered consecutively in the order in which they appear in the manuscript? **No** Is there any duplication between various parts of the manuscript and between the main text and the content presented in the figures and tables? **Not Applicable** Do the selection and design of the figures and tables follow the principles of necessity and clarity? **Yes** Are the quality and resolution of the images up to standard? **Not Applicable** Are the experimental data of the Results true and reliable? **Yes** Are the experimental data presented in the manuscript's biostatistics content reliable? **Yes** Is the description of the experiments clear and complete? **Yes** Is the content of the Materials and Methods complete? **Yes** Is the content of the Introduction adequate? **Yes** Are the Key Words complete? **Yes** Do authors' affiliations correspond to the content of the manuscript? **Yes** Does the Abstract contain the contents of each part of the manuscript (IMRaD)? **Yes** Is there any Key Word that is not included in the manuscript title? **Yes** Does the manuscript's content fall within the scope of the journal? **Yes**

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Scientific quality	Grade B (Very good)
Novelty of this manuscript	Grade B (Very Good)
Creativity or innovation of this manuscript	Grade B (Very Good)
Scientific significance of the conclusion in this manuscript	Grade A (Excellent)
Language quality	Grade A (Excellent)
Does this manuscript describe a study of the existing knowledge system?	Yes
Does this manuscript report a revolutionary innovation?	No
Does this manuscript report an unconventional innovation?	No
Conclusion	Minor revision
Re-review	Yes
Peer-reviewer statements	Peer-Review: Onymous
	Conflicts-of-Interest: No

SPECIFIC COMMENTS TO AUTHORS

I read this manuscript with great interest. The author tackle a highly relevant clinical challenge: predicting how well HCC patients will respond early on to TACE. To do this, they built a predictive model combining clinical data, conventional radiomics, and MRI-derived habitat imaging (ITH features). The results look impressive at first glance, particularly the high AUC values. That said, I have several major methodological concerns regarding patient selection, feature stability, and how the clinical outcomes were defined. These issues need to be resolved before we can consider this model robust enough for clinical implementation.

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The introduction should clearly compare the proposed approach to existing radiomics nomograms and AI models to highlight what is specifically novel (e.g., habitat construction, ecological diversity index, etc.) The authors should acknowledge that MRI-derived habitats may reflect a mixture of post-TACE lipiodol effects, perfusion, necrosis, hemorrhage, and acquisition artifacts, rather than purely tumor biology.

The authors focus exclusively on a "TACE-only" patient population. In current oncology practice, however, TACE is frequently combined with systemic therapies according international guidelines. The manuscript needs to clarify whether this model actually applies to the modern landscape of combination therapies. Also, predicting a 4-to-6-week radiographic response is practically useful, but is it a proven surrogate for overall survival or progression-free survival in this specific setting? The introduction should justify this choice. Finally, as radiologists, we should be cautious about attributing MRI habitat features purely to "tumor biology." Post-TACE imaging is notoriously messy. The features extracted likely capture a mix of lipiodol artifacts, necrosis, perfusion differences, and standard acquisition noise. The authors should acknowledge this limitation early on.

Please be aware that the submitted manuscript file contains several pages of what appears to be an internal draft or editorial notes appended after the references (frequently marked with the tag "116364_Auto_Edited-YJP"). You will likely want to clean up and remove these extraneous pages prior to the next round of revisions.

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Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 120606

Title: Imaging Tumor Heterogeneity to Predict Response to Transarterial Chemoembolization in Hepatocellular Carcinoma

Provenance and peer review: Invited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 06882639
Position: Peer Reviewer
Academic degree and professional title: MD, Postdoc
Reviewer's Country/Territory: China
Author's Country/Territory: United States

Manuscript submission date: 2026-03-02

Reviewer chosen by: Jia-Lin Zhang

Reviewer accepted review: 2026-04-04 11:03

Reviewer performed review: 2026-04-04 12:04

Review time: 1 Hour

Content to be reviewed	Does the research scope comply with ethics? **Not Applicable** Are additional experiments needed for the study? **No** Will the manuscript's content be of interest to readers? **Yes** Is the manuscript's text correct, concise, and clear? **Yes** Do authors only cite their own earlier publications? **No** Are all references related to the topic of the manuscript? **Yes**

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	manuscript? **Yes** Is there any Key Word that is not included in the manuscript title? **No** Does the manuscript's content fall within the scope of the journal? **Yes**
Scientific quality	Grade B (Very good)
Novelty of this manuscript	Grade B (Very Good)
Creativity or innovation of this manuscript	Grade B (Very Good)
Scientific significance of the conclusion in this manuscript	Grade B (Very Good)
Language quality	Grade B (Very good)
Does this manuscript describe a study of the existing knowledge system?	No
Does this manuscript report a revolutionary innovation?	No
Does this manuscript report an unconventional innovation?	No
Conclusion	Minor revision
Re-review	Yes
Peer-reviewer statements	Peer-Review: Anonymous
	Conflicts-of-Interest: No

SPECIFIC COMMENTS TO AUTHORS

The manuscript titled "Imaging Tumor Heterogeneity to Predict Response to Transarterial Chemoembolization in Hepatocellular Carcinoma" as an editorial has offered a highly critical and necessary evaluation of AI and radiomics applications in oncology. The author has systematically broken down the flaws in retrospective study

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designs, mixed imaging protocols, and statistical overfitting. However, the manuscript needs Major Revisions before publication

1. There has been a massive block of unformatted bullet points, outline notes, and placeholder tags such as "116364_Auto_Edited-YJP". This section reads like an earlier draft or an AI-generated outline. This entire section should be strictly deleted from the final manuscript, as it breaks the formal editorial structure.

2. The phrases have correctly highlighted that the original study lacked a description of missing data extent and imputation strategies. The authors should add a specific recommendation to the “Study Design and Patient Selection” section suggesting that future studies report missingness patterns and utilize multiple imputation alongside sensitivity analyses.

3. The descriptions have emphasized that predicting early response at 4 to 6 weeks lacked justification as a validated surrogate for overall survival or time-to-progression. While the authors have mention this point briefly in the main text, I think the authors should elevate this point to make it clear that without linking the model’s predictions to patient-centered endpoints the clinical utility of the habitat model remained purely theoretical.

4. The authors have critiqued regarding the use of SMDs over P-values for assessing baseline comparability was excellent. It’s better to strengthen this by briefly noting that P-values are highly dependent on sample size, making them unreliable for detecting clinically meaningful baseline imbalances in large cohorts.

5. In the “Treatment Heterogeneity” section, the authors have appropriately pointed out that treatment decisions, cTACE vs. DEB-TACE were likely based on the same tumor features that affect treatment response. Maybe the authors could mention specific clinical confounders that drive these decisions, for example, Child-Pugh score, ALBI grade, and portal hypertension, which would make this critique even more robust.

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PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 120606

Title: Imaging Tumor Heterogeneity to Predict Response to Transarterial Chemoembolization in Hepatocellular Carcinoma

Provenance and peer review: Invited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05384903
Position: Peer Reviewer
Academic degree and professional title: Associate Professor, MD
Reviewer's Country/Territory: China
Author's Country/Territory: United States

Manuscript submission date: 2026-03-02

Reviewer chosen by: Hong-Xin Jiang

Reviewer accepted review: 2026-04-13 03:43

Reviewer performed review: 2026-04-17 02:34

Review time: 3 Days and 22 Hours

Content to be reviewed	Does the research scope comply with ethics? **Yes** Are additional experiments needed for the study? **Yes** Will the manuscript's content be of interest to readers? **Yes** Is the manuscript's text correct, concise, and clear? **Yes** Do authors only cite their own earlier publications? **No** Are all references related to the topic of the manuscript? **Yes** Do authors omit important references? **No**

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Scientific quality	Grade B (Very good)
Novelty of this manuscript	Grade B (Very Good)
Creativity or innovation of this manuscript	Grade B (Very Good)
Scientific significance of the conclusion in this manuscript	Grade B (Very Good)
Language quality	Grade B (Very good)
Does this manuscript describe a study of the existing knowledge system?	Yes
Does this manuscript report a revolutionary innovation?	No
Does this manuscript report an unconventional innovation?	No
Conclusion	Minor revision
Re-review	Yes
Peer-reviewer statements	Peer-Review: Anonymous
	Conflicts-of-Interest: No

SPECIFIC COMMENTS TO AUTHORS

Reviewer Comments

This manuscript provides a commentary on the recent work by Lv et al. addressing MRI-based habitat imaging for predicting response to TACE in hepatocellular carcinoma. The topic is of clear clinical interest, particularly given the increasing attention to imaging-derived biomarkers and tumor heterogeneity in treatment decision-making. The author offers a generally thoughtful and well-informed critique, especially with regard to methodological rigor and potential barriers to clinical translation.

That said, a few points could be improved to strengthen the manuscript.

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Major Points

First, while the manuscript highlights several strengths of the original study, the discussion of its novelty could be made more precise. At present, it is not entirely clear what the author considers to be the key advance—whether it is the use of habitat imaging itself, the ecological diversity metric, or the multicenter validation. A more explicit positioning relative to prior radiomics-based prediction models would help the reader better understand what distinguishes this work.

Second, a number of methodological limitations are raised (feature selection strategy, treatment heterogeneity, outcome assessment, inter-site variability), all of which are relevant. However, they are presented somewhat uniformly, which makes it difficult to gauge their relative importance. In my view, issues related to potential information leakage during feature selection and variability in outcome definition are likely the most consequential and could be emphasized more clearly, with other points discussed more briefly.

Third, the critique of the statistical approach is generally appropriate, particularly regarding the lack of nested validation and the use of stepwise regression. That said, some of the language is rather definitive. Given that this is an editorial rather than a re-analysis, it might be preferable to frame these concerns more cautiously (e.g., "may introduce bias" rather than "introduces bias"), which would keep the tone balanced.

Fourth, the discussion around outcome definition and imaging heterogeneity is useful, especially the point about mixed CT and MRI follow-up. However, parts of this section go into quite detailed methodological alternatives (e.g., modeling outcomes as ordinal or continuous), which may be more than necessary for this format. The core message—potential misclassification and lack of reported inter-reader agreement—is already strong and could stand on its own.

Finally, the section on clinical relevance would benefit from being a bit more concrete.

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The manuscript notes that TACE is increasingly used in combination with systemic therapies, but it remains somewhat unclear how the proposed model might fit into current clinical workflows. A brief discussion of potential use cases (for example, pre-treatment stratification versus early response assessment) and how this approach compares with existing prognostic tools would make this section more practical.

Minor Points

- Some paragraphs, particularly those dealing with statistical considerations, are quite dense and could be shortened slightly for readability.
- The use of terms such as “generalizability” and “transportability” is somewhat interchangeable; it may be helpful to standardize or clarify their use.
- A few statements (e.g., describing certain limitations as “critical”) could be softened to maintain a more neutral tone.
- The reference list is appropriate, although a small degree of consolidation might improve flow.

Recommendation

Overall, this is a solid and relevant commentary that raises important points about methodology and clinical applicability. With some refinement in emphasis, tone, and clarity, it would be suitable for publication.

Recommendation: Minor revision

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RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 120606

Title: Imaging Tumor Heterogeneity to Predict Response to Transarterial Chemoembolization in Hepatocellular Carcinoma

Provenance and peer review: Invited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 08040211
Position: Peer Reviewer
Academic degree and professional title: Associate Professor, MD
Reviewer's Country/Territory: Chile
Author's Country/Territory: United States

Manuscript submission date: 2026-03-02

Reviewer chosen by: Xin-Yue Hu

Reviewer accepted review: 2026-04-22 01:02

Reviewer performed review: 2026-04-22 01:14

Review time: 1 Hour

Content to be reviewed	Does the research scope comply with ethics? **Not Applicable** Are additional experiments needed for the study? **No** Will the manuscript's content be of interest to readers? **Yes** Is the manuscript's text correct, concise, and clear? **Yes** Do authors only cite their own earlier publications? **No** Are all references related to the topic of the manuscript? **Yes**

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	Is there any Key Word that is not included in the manuscript title? **Yes** Does the manuscript's content fall within the scope of the journal? **Yes**
Scientific quality	Grade B (Very good)
Novelty of this manuscript	Grade C (Good)
Creativity or innovation of this manuscript	Grade B (Very Good)
Scientific significance of the conclusion in this manuscript	Grade B (Very Good)
Language quality	Grade A (Excellent)
Does this manuscript describe a study of the existing knowledge system?	No
Does this manuscript report a revolutionary innovation?	No
Does this manuscript report an unconventional innovation?	No
Conclusion	Accept
Peer-reviewer statements	Peer-Review: Anonymous
	Conflicts-of-Interest: No

SPECIFIC COMMENTS TO AUTHORS

Arunkumar Krishnan submitted the reviewed version of the manuscript titled: Imaging Tumor Heterogeneity to Predict Response to Transarterial Chemoembolization in Hepatocellular Carcinoma.

After carefully revising the manuscript, I thank the author for addressing the concerns raised during the peer-review process.