

**Dear valuable Editorial Board and reviewers of World Journal of Transplantation:**

Many thanks again for your kind and valuable revision of our manuscript entitled:

**Challenges related to clinical decision-making in hepatocellular carcinoma Recurrence post-liver transplantation: Is there a hope?**

Here is a Point-by-Point response of how we complied with each request including the page number where the revision occurred, and the addition highlighted in the text:

**Reviewer #1 comments:**

**Scientific Quality:** Grade A (Excellent)

**Language Quality:** Grade A (Priority publishing)

**Conclusion:** Accept (High priority)

**Specific Comments to Authors:**

Thank you very much for this interesting review. I have some questions and remarks. For the first one, is there any immunohistochemistry marker like Ki 67 to distinguish between proliferative and non proliferative type?. The term "under the umbrella" is too much used. Can you replace it by an other expression to avoid it's repetition?.

Response: Your comments are much appreciated and highly considered; a change has been done as the following (page 3/5/7/8/9).

1. Regarding the 2 major HCC subclasses, they have been identified through integrated criteria of histological features, transcriptomic analysis, and genetic aberrations; The proliferative variant is most often poorly differentiated, associated with chromosomal instability/TP53 mutations, and even include cancer cells with progenitor features. On the contrary, the non-proliferative subgroup mainly displays a well-differentiated phenotype with chromosomal stability and preserved hepatocytic markers expression.
2. The term "under the umbrella" has been reduced and replaced in the whole manuscript:
  - A) postoperative morbidity (60–80%) with a high risk of infections owing to immunosuppression intake
  - B) However, the definite indications of various systemic therapies in the presence of immunosuppressants in post-transplant patients with tumour recurrence are still complex
  - C) as both adaptive and concomitant immunity are suppressed under the coverage of post-transplant immunosuppression which is essential in preventing graft rejection and loss.
  - D) owing to the immune system inability in case of CNIs intake to detect and destroy circulating/latent tumour cells

E) including a complete tumour staging and the suitable therapeutic option in the settings of immunosuppression intake, till being universally standardized as guidelines in the international liver societies.

**Reviewer #2 comments:**

Reviewer #2:

**Scientific Quality:** Grade A (Excellent)

**Language Quality:** Grade A (Priority publishing)

**Conclusion:** Accept (High priority)

**Specific Comments to Authors:**

Good work. Thank you for your contributions in this field.

Response: Your comments are highly considered and appreciated.

**Editorial Office's comments and suggestions, which are provided below:**

**(1) Science Editor:**

**1 Scientific quality:** The authors submitted a review of challenges related to clinical decision-making in hepatocellular carcinoma recurrence post-liver transplantation.

(1) **Classification:** Grade A and Grade A;

(2) **Summary of the Peer-Review Report:** For the first one, is there any immunohistochemistry marker like Ki 67 to distinguish between proliferative and non proliferative type?. The term "under the umbrella" is too much used;

(3) **References recommendations:** The reviewer didn't request the authors to cite improper references published by him/herself.

(4) **Manuscript Type:** After verification, the manuscript type is "Minireviews".

**2 Specific comments**

(1) **Country/Territory of origin:** Egypt.

(2) **Please add the Running Title:** A short running title of no more than 6 words should be provided. Abbreviations are permitted. **For example,** Losurdo G *et al.* Two-year follow-up of HCC.

(3) **Author contributions does not meet the requirements:** The 'Author contributions' passage describes the specific contribution(s) made by each author. The author's names will be listed in the following format: full family (sur)name, followed by abbreviated first and middle names. For example, Bryan L Copple should be revised as Copple BL. A full multi-author example is: Wang CL, Liang L, Fu JF, Zou CC, Hong F and Wu XM designed the research study; Wang CL, Zou CC, Hong F and Wu XM performed the research; Xue JZ and Lu JR contributed new reagents and analytic tools; Wang

CL, Liang L and Fu JF analyzed the data and wrote the manuscript; All authors have read and approved the final manuscript.

(4) **The “Key Words” does not meet the requirements:** Please do not use abbreviations for the keywords (*e.g.*, Ulcerative colitis, not UC). The first letter of each keyword will be capitalized, and each keyword will be separated by a semicolon, with no terminal period. **An example of correct formatting is:** Non-alcoholic fatty liver disease; Alcoholic liver disease; Non-alcoholic steatohepatitis; Insulin resistance; Oxidative stress.

(5) **Please add the “Core Tip”.** The Core Tip is a short paragraph that is independent of the content of the Abstract. The ‘Core Tip’ will provide a succinct summary of the study that outlines its most innovative and important arguments. This section should be less than 100 words. Abbreviations must be defined upon first appearance in the Core Tip. Do not use non-standard abbreviations, unless they appear at least two times in the text preceding the first usage/definition.

**An example of correct formatting is:**

In this study, CellChat was employed to infer cell-cell communication, thereby selecting highly active cell groups in immune-related pathways on single-cell RNA-sequencing data. Highly active immune cells were identified by intersecting these groups with B and T cells. Subsequently, significantly differentially expressed genes between highly active immune cells and the remaining cells were incorporated into the Lasso regression model. Ultimately, incorporating genes selected more than 5 times in 10 Lasso regression experiments into a multivariable Cox regression model, 3 genes (stathmin 1, cofilin 1, and C-C chemokine ligand 5) significantly associated with survival were identified to construct a gene signature.

(6) **Reference numbers in the main text.**

The format of in-text citation of references should be [References Number], which should be with no space between “[ ]” and the preceding word. **Example:** The pathophysiology is thought to be due to an increased arterial flow that leads to secondary hepatocellular hyperplasia[1,2].

If the name of the author(s) of a reference is listed in the sentence, the reference number should be placed immediately after the author(s) of the reference. **Example:** Mandal *et al*[8] proposed that retractor aponeurosis disinsertion is the most likely cause of congenital low lid entropion.

(7) **There are issues with the references:**

Please provide the PMID numbers (<https://pubmed.ncbi.nlm.nih.gov/>) and DOI citation numbers (<https://doi.crossref.org/simpleTextQuery>) to the reference list and list all authors of the references. If a reference has no PMID and DOI, please provide the source website address of this reference.

To ensure the accuracy of the references, please use "**Edit References by Auto-Analyser**" (<https://www.f6publishing.com/Forms/main/ArticleReferenceTool.aspx>) to edit the references of the manuscript.

(8) **Tables. The Table title needs to be bolded.**

Authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.

The title "Table 1" or "Table 2" does not require adding a period or colon, and the table title does not have a period or colon. For example, "**Table 2 Characteristics of the studies included in the meta-analysis**".

(9) **Main text.** The first level subtitles should be all capitalized, bolded and underlined. For example: "**INTRODUCTION**".

Under each first-level subtitle, there can be several second-level subtitles. For formatting, capitalize the first letter for the first word; the subtitles are all in bold and italicized. For example: "***Use of anti-inflammatory agents***".

There can be several third-level subtitles under the second-level subtitles. For these, the first letter of the first word is capitalized, and the full subtitles are bolded followed by a colon immediate. For example: "**Mechanism of liver cancer: ...**".

(10) It is not allowed to add a sequence number before first level subtitles, second level subtitles, and third level subtitles. For example: "**1 INTRODUCTION**". **Please delete '1'**.

(11) Regarding abbreviations, please do not list them separately. Abbreviations must be defined at the first occurrence. For example, when CT first appears in the manuscript, please use the format "computed tomography (CT)".

**3 Recommendation:** Conditional acceptance.

Language Quality: Grade A (Priority publishing)

Scientific Quality: Grade A (Excellent)

Response: Your comments are much appreciated and highly considered;

I. **Regarding the valuable peer reviewers' comments**, it has been carefully addressed and a change has been done as the following (page 3/5/7/8/9).

1. Regarding the 2 major HCC subclasses, they have been identified through integrated criteria of histological features, transcriptomic analysis, and genetic aberrations; The proliferative variant is most often poorly differentiated, associated with chromosomal instability/TP53 mutations, and even include cancer cells with progenitor features. On the contrary, the non-proliferative subgroup mainly displays a well-differentiated phenotype with chromosomal stability and preserved hepatocytic markers expression.
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  - D) owing to the immune system inability in case of CNIs intake to detect and destroy circulating/latent tumour cells
  - E) including a complete tumour staging and the suitable therapeutic option in the settings of immunosuppression intake, till being universally standardized as guidelines in the international liver societies.

II. **Regarding the running title**, it has been added as the following (page 1):

Short title: Management of recurrent HCC post-LT

III. **Regarding the Author contributions statement**, it has been revised and corrected to meet the requirements as the following (page 9):

Badwei N. collected, designed the research data, and wrote the manuscript with critical final revision and editing.

IV. **Regarding the “Key Words”**, it has been revised and corrected to meet the requirements as the following (page 1):

**Keywords:** Hepatocellular carcinoma; Recurrence; Liver transplantation; Prognosis; Clinical decisions; Management.

V. **Regarding the “Core Tip” paragraph**, it has been added to meet the requirements as the following (page 1):

In this review, challenges and debates related to the management of Hepatocellular carcinoma (HCC) recurrence after liver transplantation (LT) were carefully handled, discussing the risk factors, pre/post-LT prediction models of tumor recurrence, and different therapeutic approaches either curative or ablative in the settings of post-LT immunosuppression.

VI. **Regarding the reference numbers in the main text**, it has been revised and corrected in the whole manuscript to meet the requirements as the following (page 2/3/4/5/6/7/8/9)

VII. **Regarding the references**, it has been revised and corrected to meet the requirements as the following (page 10-18)

VIII. **Regarding the table**, it has been revised and corrected to meet the requirements in the whole manuscript as the following (page 19)

IX. **Regarding the subtitles**, it has been revised and corrected to meet the requirements in the whole manuscript as the following (page 2-10)

X. **Regarding the abbreviations**, it has been revised and corrected to meet the requirements in the whole manuscript as the following (page 2-10)

**(2) Company Editor-in-Chief:**

I have reviewed the Peer-Review Report, full text of the manuscript, all of which have met the basic publishing requirements of the **World Journal of Transplantation**, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors

Response: Your comments are much appreciated and highly considered; The whole manuscript have been revised according to the recommendation of valuable peer-Review Report, Editorial Office's comments (highlighted and discussed in the reply letter and the manuscript text)

Sincerely,