

Dear Reviewer 1,

Thank you for your insightful comments on our manuscript. We appreciate your recognition of the extensive effort put into this review and your valuable feedback has made the following revisions:

1. The abstract should be more concise and directly highlight the main findings and conclusions. Currently, it reads more like a background introduction rather than a summary of the paper's core content.

Response: We want to thank the reviewers for their valuable comments. The previous summary was indeed too verbose, and we removed some common sense and repetition of the following words to make the summary more concise. For example, *Cirrhosis is a pathological entity characterized by diffuse liver fibrosis, and after entering the decompensated stage, patients often have abnormal liver function and portal hypertension.* The abstract has been modified to highlight the main findings and conclusions more directly: **1. Liver regeneration in patients with cirrhosis can promote the occurrence of re-compensation, thereby improving the prognosis of patients. 2. Monitoring liver regeneration indicators helps us assess patients' re-compensation potential for early selection of appropriate treatment options.** Thank you again for your constructive suggestions.

2. The introduction provides a good background on cirrhosis and its progression, but lacks recent references to support the changing perspective on reversibility. Incorporate recent high-impact studies to strengthen the argument.

Response: We would like to thank the reviewers for their valuable comments. It is true that the previous introduction only expounds the existing viewpoint and does not incorporate the relevant literature, which seems to be unconvincing. With revisions, we have attached some recent literature that

can support the re-compensation of cirrhosis with treatment of the cause, specifically: In a prospective cohort study by Premkumar *et al* [4], 1152 patients with hepatitis C virus (HCV)-associated decompensated cirrhosis, 284 (24.7%) achieved re-compensation after treatment with effective direct-acting antivirals; In a multicenter prospective study by Wang *et al* [5], 56.2%(159/283) of patients with hepatitis B virus (HBV)-associated cirrhosis decompensated achieved re-compensation after 120 wk of antiviral therapy; An observational study by Hofer *et al* [6] on decompensated alcohol-related cirrhosis showed that persistent abstinence resulted in hepatic re-compensation in 18.1% (37/204) of patients. These literatures have proved the reversibility of liver cirrhosis and strengthened the persuasiveness of the article. Thank you again for your constructive suggestions.

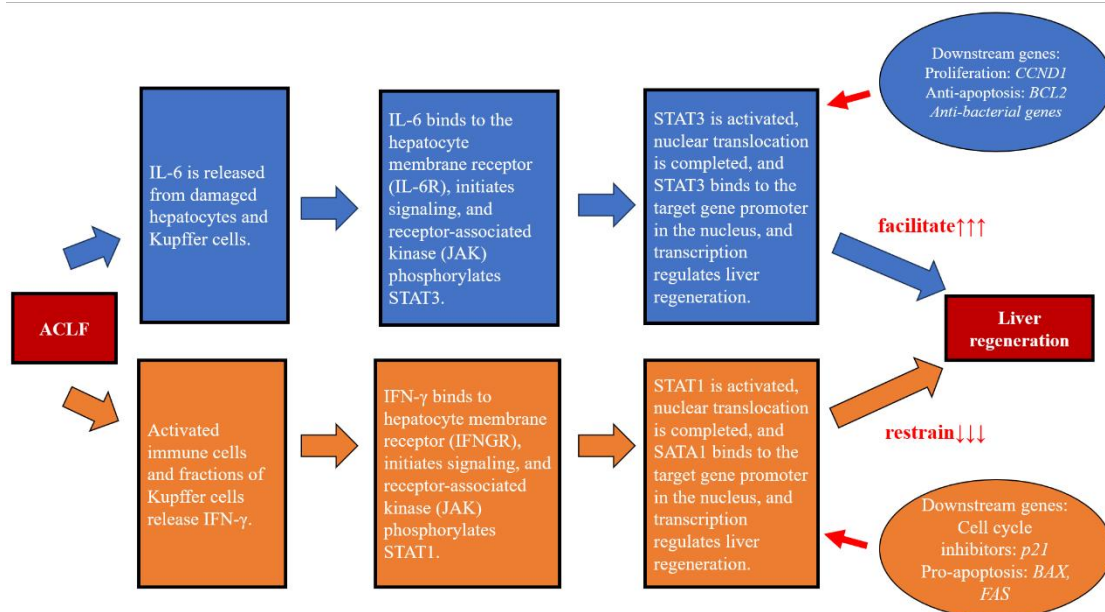
3. The introduction could benefit from a clearer statement of the research gap and the paper's objectives.

Response: We would like to thank the reviewers for their valuable comments. It is true that the previous discussion in the introduction is relatively vague and superficial, and does not fully reflect the gap with other studies and the objectives of the paper. With modifications, we have clarified the shortcomings of existing research and the need to assess the potential for patient recompensation, such as: **For patients with high re-compensation potential, patients should be encouraged to continue active etiological treatment, anti-inflammatory, anti-fibrotic therapy, and prevention and treatment of complications if necessary, to promote hepatocyte repair and regeneration, to improve the quality of life of patients; For those who are unlikely to achieve re-compensation, they should be prepared for liver transplantation in the long term.** At present, some studies have pointed out that gender, severity of liver disease, severity of portal hypertension, systemic inflammatory response, and other factors may affect the re-compensation of patients with decompensated liver cirrhosis. However, the predictive value of

liver regeneration on re-compensation in existing studies has been neglected. Therefore, this article aims to review the value of liver regeneration in the re-compensation of decompensated cirrhosis. After filling and organizing the content, the context is more logical than before, and the core purpose of this article is more prominent. Thank you again for your constructive suggestions.

4. Present results using tables, figures, and statistical significance levels to enhance readability and clarity.

Response: We would like to thank the reviewers for their valuable comments. We strongly agree that tables and graphs can significantly improve the readability and clarity of an article. Before the revision, this article had a table summarizing how to assess re-compensation in clinical practice from multiple dimensions. After the revision, a schematic diagram of two pathways related to liver regeneration in ACLF was added according to the article's content. This diagram can help readers understand how the human body balances the liver's regeneration ability after acute liver injury, based on cirrhosis. The quality of this schematic is still insufficient, and I would be happy to refine it in future revisions. Thank you again for your constructive suggestions.



5. The discussion section should delve deeper into the implications of the

findings and how they contribute to the existing knowledge on liver regeneration and cirrhosis.

Response: We would like to thank the reviewers for their valuable comments. Before the revision, the discussion of existing research and the outlook for the future in this paper were superficial and general. Thank you again for your constructive suggestions. After the revision, I have added more reference articles to support my point of view and point out the direction of future research development more clearly. For example, existing studies can suggest the feasibility of recompensation for some rare causes of cirrhosis. However, there is still a lack of high-quality data to support it, and further studies in patients with cirrhosis of various etiologies are needed in the future to increase the versatility of recompensation. Specifically: **Hofer *et al* [19] defined the criteria for etiological treatment success as normalization of bilirubin and alkaline phosphatase (ALP) reduced to ≤ 1.5 times the upper limit of normal (ULN) (determined to be a biochemical response to UDCA by reference to Paris II criteria) with ursodeoxycholic acid (UDCA, the first-line agent for PBC), and 7 patients (16.7%) received re-compensation. Another pilot study demonstrated that decompensated cirrhosis due to autoimmune hepatitis (AIH) can achieve re-compensation in some patients after successful immunosuppressive therapy (4/21) [20]. These studies have small sample sizes, limited statistical power, and limited extrapolation of results. However, they also suggest the feasibility of re-compensation in cirrhosis of multiple etiologies, which still needs further study.** For example, in the chapter **LIVER REGENERATION AFTER LIVER INJURY**, the IL-6/STAT3 pathway and IFN- γ /STAT1 pathway that regulate liver regeneration are further elaborated based on the original basis, and their therapeutic significance is pointed out. The significance of each study has been further elaborated, and the future outlook has been more concrete. Thank you again for your constructive suggestions.

6. The conclusion should be more concise and directly summarize the main findings and their significance.

Response: We would like to thank the reviewers for their valuable comments. Once again, we thank you for your constructive suggestions. We've condensed the conclusions and removed some sentences that resemble background introductions, such as: **Traditionally, cirrhosis has been regarded as a point of no return from compensated to decompensated, and once a decompensated event occurs, the average survival of patients will be seriously threatened.** We summarize the core conclusion of the article: **1. The recovery of liver regeneration ability in patients with cirrhosis can promote the occurrence of recompensation and improve the patient's prognosis. 2. We should actively maintain the liver regeneration ability of patients with decompensated cirrhosis to promote the occurrence of re-compensation and further improve the clinical evaluation methods on hepatocyte regeneration.**

Thank you again for your constructive suggestions.

7. Use consistent terminology throughout the paper to avoid confusion. For example, clarify the distinction between "recompensation" and "liver regeneration."

Response: We would like to thank the reviewers for their valuable comments. We systematically optimize the presentation of the full text to avoid confusion among readers. Recompensation is the return of patients with cirrhosis from decompensation to compensation after effective treatment of the cause, including a long period of absence of decompensation events and improvement of liver function. Liver regeneration is the reconstruction of liver structure and function after liver injury. Hepatocyte regeneration may be one of the pathophysiological mechanisms of recompensation, which may indicate the recompensatory potential of patients. Thanks again for your

constructive suggestions.

8. Suggest updating the reference list to include recent and relevant publications that support the study's findings or provide additional context for the research. The following paper PMID: 39276679, 39185304 and 39081955 may be helpful.

Response: We would like to thank the reviewers for their valuable comments.

This article has added "DOI:10.1016/s0168-8278(24)01151-6" , DOI:10.1016/j.jhep.2019.11.013" and other literature to further enrich the article's content. Thank you for providing the recommended literature. Although I did not directly quote the articles you provided, after careful reading, these articles strengthened my understanding of cirrhosis and allowed me to optimize the article's content further. Again, thank you for your constructive suggestions.

9. Ensure that complex medical terms are defined or explained in simple language to enhance readability for a broader audience.

Response: We would like to thank the reviewers for their valuable comments.

As you said, some complex medical terms, such as **IL-6/STAT3 pathway and IFN- γ /STAT1 pathway**, have not been further explained in this article. To improve readability for a wider audience, additional explanations are provided when citing complex medical terms, such as: **STAT3 and STAT1 are both members of the STAT protein family and are key intracellular signal transduction proteins, which are complementary and often antagonistic. IL-6 and IL-22 predominantly activate STAT3, and IFN- γ predominantly activates STAT1.** After the explanation, we believe it is more conducive to the reader's understanding of the article. Thanks again for your constructive suggestions.

Dear Reviewer 2,

Thank you for your insightful comments on our manuscript. We appreciate your recognition of the extensive effort put into this review and your valuable feedback. We have made the following revisions:

1. **Lack of Novelty:** While the link between liver regeneration and recompensation is highlighted, the review largely reiterates existing knowledge without proposing novel mechanisms, therapeutic targets, or frameworks. For example, AFP 's role as a regeneration marker is well-documented; deeper exploration of how AFP-driven regeneration structurally reverses fibrosis would enhance originality. - **Limited Mechanistic Insights:** The discussion of pathways (e.g., IL-6/STAT3 vs. IFN- γ /STAT1) is superficial. A detailed schematic summarizing molecular pathways driving regeneration in cirrhosis could improve clarity. - **Overreliance on HBV Studies:** Most cited data focus on HBV-related cirrhosis. Broader inclusion of other etiologies (e.g., MAFLD, autoimmune) would strengthen generalizability.

Response: We would like to thank the reviewers for their valuable comments. As you noted, this review does not clarify new mechanisms, therapeutic targets, or frameworks. Therefore, this paper refers to the articles [doi: 10.1016/j.gendis.2020.07.01] and [doi: 10.1016/j.jhep.2019.11.013] to further elucidate the potential therapeutic targets of liver regeneration in patients with liver cirrhosis from the mechanism and make a schematic diagram. Specifically: The study by Nakano *et al* [16] identified a unique population of AFP-expressing cells induced by Jagged1/Notch2 signaling in mouse fibrotic liver. It was found that in fibrotic liver tissues, the expression of Jagged1 (ligand protein) in myofibroblasts was significantly increased, which stimulated the Notch2 (receptor protein) signaling of adjacent

AFP-expressing cells, thereby inducing the mobilization and proliferation of AFP-expressing cells. These AFP-positive cells exhibit the characteristics of immature hepatocytes and have high proliferative capacity, which may contribute to the regeneration of fibrotic liver and are associated with the prolonged survival time after partial hepatectomy in mice with fibrotic liver. Acute-on-chronic liver failure (ACLF) is an acute liver injury and rapid deterioration of liver function based on chronic liver disease, often complicated by bacterial infection, and its short-term mortality rate is high. Xiang *et al* [17] found that liver fibrosis and bacterial infection had significant inhibitory effects on liver regeneration induced by acute liver injury by constructing a mouse model of ACLF, which was achieved by impairing the IL-6/signal transduction and activator of transcription (STAT)3 pathway, which promotes regeneration and enhancing the interferon (IFN)- γ /STAT1 pathway, which inhibit regeneration. STAT3 and STAT1 are both members of the STAT protein family and are key intracellular signal transduction proteins, which are complementary and often antagonistic. IL-6 and IL-22 predominantly activate STAT3, and IFN- γ predominantly activates STAT1. The balance of the two plays a key role in controlling liver damage and regeneration (Figure 1). IL-22Fc is a recombinant fusion protein consisting of two human IL-22 molecules linked to a constant region of immunoglobulin. IL-22Fc has been found to activate STAT3 and attenuate STAT1 in the liver, promoting liver regeneration and mitigating bacterial infections to improve ACLF survival. It can be seen that effective restarting of liver regeneration in patients with cirrhosis is essential to improve the prognosis, and adjusting the signaling pathways related to liver regeneration is a therapeutic strategy worthy of our consideration. I don't think this aspect is deep enough, and I'd be happy to make further changes.

In addition, since most of the existing relevant studies are based on HBV-related cirrhosis, most of the literature cited in this study is HBV-related

cirrhosis, and there is a lack of inclusion of other etiologies. As a result, some research data on patients with cirrhosis associated with other causes have been added, such as: Hofer *et al* [19] defined the criteria for etiological treatment success as normalization of bilirubin and alkaline phosphatase (ALP) reduced to ≤ 1.5 times the upper limit of normal (ULN) (determined to be a biochemical response to UDCA by reference to Paris II criteria) with ursodeoxycholic acid (UDCA, the first-line agent for PBC), and 7 patients (16.7%) received re-compensation. Another pilot study demonstrated that decompensated cirrhosis due to autoimmune hepatitis (AIH) can achieve re-compensation in some patients after successful immunosuppressive therapy (4/21) [20]. These studies have small sample sizes, limited statistical power, and limited extrapolation of results. However, they also suggest the feasibility of re-compensation in cirrhosis of multiple etiologies, which still needs further study. I don't think it's broad enough in this area, and I'd be happy to make additional revisions. Thanks again for your constructive suggestions.

2. Methodology and Data Presentation Strengths: - Table 1 provides a structured overview of recompensation assessment dimensions. Weaknesses: - Incomplete Validation: The BC2AID and TACIA scores are mentioned but lack validation across diverse cohorts. Highlighting limitations (e.g., HBV-centric validation) is necessary. - Ambiguous Definitions: The Baveno VII criteria's liver function parameters (ALB, INR, bilirubin) lack standardized cut-offs. A comparative analysis of proposed thresholds (e.g., Wang et al. vs. Baveno VII) is needed. -Underdeveloped Table 1: The "Assessment methods" column is overly vague. For example, "precursor cell markers" should specify clinical assays (e.g., EpCAM/CK19 immunohistochemistry) and their feasibility.

Response: We would like to thank the reviewers for their valuable comments.

As you said, there is still a lack of validation of the BC2AID and TACIA scores in different cohorts, and it is necessary to highlight the limitations given the inadequacy of the existing studies. Specifically: **However, both the BC2AID score and the TACIA score still lack validation in different large and diverse cohorts, and the scores are all based on patients with HBV-related liver disease. In contrast, patients with other causes of liver disease are not included. In the future, the predictive value of AFP, platelets, and other indicators on re-compensation should be further studied in patients with liver cirrhosis caused by different etiologies (including alcoholic, autoimmune, etc.), to build a more versatile clinical prediction model.** Regarding the recompensation of liver function, the liver function parameters (ALB, INR, bilirubin) proposed by the Baveno VII criteria do not define standardized cut-offs. In this regard, different studies have used different criteria. Wang et al.'s study suggests thresholds, but they are still limited. The revisions list the definitions of different standards, specifically: **Wang *et al* [4] proposed a precise definition of stable improvement in liver function [model for end-stage liver disease (MELD) score < 10 and/or Child-Pugh class A, i.e., ALB > 35 g/L and INR < 1.50 and total bilirubin (TBIL) < 34 μmol/L]. This was included in China's latest *Guidelines for the Prevention and Treatment of Chronic Hepatitis B* (version 2022). However, that study only included patients with HBV-related decompensated cirrhosis treated with entecavir, and it is still unclear whether these criteria can be applied to other causes of cirrhosis or other treatments.** Further comparisons may be needed between the pros and cons of the different criteria, which I would be happy to refine in the future.

As you mentioned, the previous description of precursor cell markers in clinical application was too vague, and the revised description details how precursor cell markers should be detected in the clinic. Specifically: **Liver biopsy tissue can be used in clinical practice to perform immunohistochemistry, intuitively localize precursor cells expressing**

specific markers, and evaluate their distribution and number. The increase in marker-positive cellularity in chronic liver disease/cirrhosis may indicate compensatory activation of liver precursor cells, while sustained high expression may indicate the risk of liver failure or a tendency to cancer. However, this operation requires an invasive biopsy and is unsuitable for dynamic monitoring. Serological markers, such as soluble CK19 fragments (CYFRA21-1) and EpCAM ectodomain (EpEX) in the serum, can also be detected through enzyme-linked immunosorbent assays (ELISA). They can be dynamically monitored to observe peaks and downward trends to evaluate regeneration. However, serum markers have low sensitivity and specificity, and interference from other diseases, such as malignant tumors, is required. The clinical application is limited. Thanks again for your constructive suggestions.

3. Structure and Readability Strengths: - The manuscript is logically organized, with clear sections (e.g., liver regeneration mechanisms, recompensation criteria). Weaknesses: -Redundancy: Sections on AFP's prognostic value (e.g., paragraphs in "Role of Liver Regeneration") repeat similar points. Consolidate these into a focused subsection. -Overly Technical Language: Terms like "liver progenitor cells (LPCs)" and "STAT3 pathway" are introduced without sufficient context for non-specialists. A glossary or simplified explanations would aid readability. - Inconsistent Terminology: Use of "recompensation" vs. "re-compensation" should be standardized.

Response: We would like to thank the reviewers for their valuable comments. As you said, the structure of this article needs to be optimized, and the content in different chapters is duplicated. Therefore, the position of some content has been adjusted, duplicate content has been removed, and the article's structure has been optimized. For overly specialized medical terms, detailed explanations have been attached to the use of the vocabulary.

"recompensation" has been replaced by "re-compensation" in the full text. Thanks again for your constructive suggestions.

4. Future Directions and Clinical Relevance Strengths: - The call for individualized treatment strategies and regenerative capacity monitoring is clinically relevant. Weaknesses:- Unclear Research Gaps: Future directions (e.g., "further research on liver histopathology") are too generic. Specify actionable priorities (e.g., validating AFP in MAFLD cohorts, exploring IL-22 therapy). - Underdeveloped Clinical Applications: How can clinicians practically assess liver regeneration (e.g., AFP thresholds, imaging protocols)? Provide actionable recommendations.

Response: We would like to thank the reviewers for their valuable comments. As you said, the previous statements in this regard were too general. The chapter *Liver cirrhosis re-compensation was evaluated in combination with the liver regeneration index, which* has been added to explain how to assess liver regeneration from the aspects of serological markers, imaging, liver biopsy, etc., to enhance clinical relevance.

I have more practical suggestions for the future direction of the research. For example: **However, both the BC2AID score and the TACIA score still lack validation in different large and diverse cohorts, and the scores are all based on patients with HBV-related liver disease. In contrast, patients with other causes of liver disease are not included. In the future, the predictive value of AFP, platelets, and other indicators on re-compensation should be further studied in patients with liver cirrhosis caused by different etiologies (including alcoholic, autoimmune, etc.), to build a more versatile clinical prediction model.** The revised content can somewhat guide future research, but it is still not in-depth enough, and I am happy to modify it further. Thanks again for your constructive suggestions.

5. Ethical and Technical Concerns - Referencing: The references are

comprehensive but should be checked for proper formatting consistency. Some references have incorrect formatting of DOIs and PMID numbers. Additionally, some older references could be balanced with more recent studies to reflect the latest advancements in the field.

Response: The format of the references has been corrected, and some references have been added, such as DOI: 10.1016/s0168-8278(24)01151-6, DOI: 10.1016/j.jhep.2019.11.013.

6. Language and Grammar - Minor Errors: -"recompensation" vs. "re-compensation" (standardize). - Awkward phrasing: "This also indicates that, in addition to the severity of liver injury, liver regeneration is a key determinant of liver failure prognosis." Recommendation Major Revision Required The manuscript addresses an important topic but requires substantial revisions to enhance originality, methodological clarity, and clinical applicability.

Response: Word misuse has been corrected, and the language expression of the whole text has been optimized.

Specific recommendations include: 1. Mechanistic Depth: Elaborate on molecular pathways (e.g., IL-6/STAT3) and their therapeutic implications. 2. Data Expansion: Include non-HBV etiologies and validate prognostic models in diverse cohorts. 3. Structural Refinement: Consolidate repetitive sections, simplify jargon, and standardize terminology. 4. Future Directions: Propose specific research priorities (e.g., regenerative biomarkers for MAFLD).

Response: This suggestion is a summary of the above suggestion, and the article's content has been improved due to the above revisions. Thank you again for your constructive suggestions and for the great help you have given me.