



## PEER-REVIEW REPORT

**Name of journal:** *World Journal of Hepatology*

**Manuscript NO:** 109093

**Title:** Hepatic osteodystrophy-An underrecognized metabolic bone disease

**Provenance and peer review:** Invited Manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer's code:** 08501193

**Position:** Peer Reviewer

**Academic degree and professional title:** MD, PhD

**Reviewer's Country/Territory:** China

**Author's Country/Territory:** India

**Manuscript submission date:** 2025-04-28

**Reviewer chosen by:** Hong-Xin Jiang

**Reviewer accepted review:** 2025-05-07 10:18

**Reviewer performed review:** 2025-05-13 13:46

**Review time:** 6 Days and 3 Hours

<b>Content to be reviewed</b>	Does the manuscript's content fall within the scope of the journal? <b>Yes</b> Do authors' affiliations correspond to the content of the manuscript? <b>Yes</b> Is there any Key Word that is not included in the manuscript title? <b>No</b> Does the Abstract contain the contents of each part of the manuscript (IMRaD)? <b>Yes</b> Are the Key Words complete? <b>Yes</b> Is the content of the Introduction adequate? <b>Yes</b>
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**https://**www.wjgnet.com

Is the content of the Materials and Methods complete?

**Not Applicable**

Is the description of the experiments clear and complete? **Not Applicable**

Are the experimental data presented in the manuscript's biostatistics content reliable? **Not Applicable**

Are the experimental data of the Results true and reliable? **Not Applicable**

Are the quality and resolution of the images up to standard? **Yes**

Do the selection and design of the figures and tables follow the principles of necessity and clarity? **Not Applicable**

Is there any duplication between various parts of the manuscript and between the main text and the content presented in the figures and tables? **No**

Are the figures and tables numbered consecutively in the order in which they appear in the manuscript? **Yes**

Is the content of the Discussion reasonable? **Yes**

Are all references necessary and reasonable? **Yes**

Is the Conclusion reasonable? **Yes**

Do authors omit important references? **No**

Are all references related to the topic of the manuscript? **Yes**

Do authors only cite their own earlier publications? **No**

Is the manuscript's text correct, concise, and clear? **Yes**

Will the manuscript's content be of interest to readers? **Yes**

Are additional experiments needed for the study? **No**



	Does the research scope comply with ethics? <b>Not Applicable</b>
Scientific quality	Grade A (Excellent)
Novelty of this manuscript	Grade B (Very Good)
Creativity or innovation of this manuscript	Grade C (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	Major revision
Re-review	Yes
Peer-reviewer statements	Peer-Review: Anonymous
	Conflicts-of-Interest: No

### SPECIFIC COMMENTS TO AUTHORS

The manuscript entitled “Hepatic osteodystrophy - An underrecognized metabolic bone disease” provides a comprehensive minireview of the role of hepatic osteodystrophy. Hepatic osteodystrophy is a common and frequently untreated complication, manifested as osteoporosis or osteopenia, encountered in the evolution of chronic liver diseases. The authors have done an extensive literature review, covering various aspects of hepatic osteodystrophy, such as pathogenesis, management and further research direction. The topic is highly relevant and interesting. However, there are several areas where the



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manuscript could be improved to enhance its quality. 1. Do different types of chronic liver disease lead to hepatic osteodystrophy through different pathogenetic pathway or mechanism? 2. The authors discussed a lot of molecular pathways in the pathogenesis of hepatic osteodystrophy, such as IGF-1, IGFBP-3, Wnt/ $\beta$ -catenin signaling pathway and RANKL/OPG. Please show these mechanisms more clearly in Figure 1. 3. Are there any interactive effects among different physiological events during the pathogenesis of hepatic osteodystrophy? 4. Please review figure 2. Does parathyroid hormone only have the positive effects on osteoblast? How about the effects of parathyroid hormone on osteoclast? 5. In figure 2. Please add how hepatic stellate cells transform into activated hepatic stellate cells. Please add the source of tumor necrosis factors which activate T cells. 6. Please further discuss how to integrate hepatic osteodystrophy therapy into regular chronic hepatic disease management? Overall, the manuscript entitled "Hepatic osteodystrophy - An underrecognized metabolic bone disease" is a valuable contribution to the field, providing a detailed overview of the pathogenesis and management of hepatic osteodystrophy. However, it would benefit from a more critical analysis of the existing literature, a deeper discussion of treatment options, and a more detailed roadmap for future research. With these improvements, the manuscript could serve as a more comprehensive and balanced review for researchers and clinicians interested in hepatic osteodystrophy and modern molecular biology.



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**Provenance and peer review:** Invited Manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer’s code:** 04213406

**Position:** Editorial Board

**Academic degree and professional title:** Associate Professor, MD, PhD

**Reviewer’s Country/Territory:** Egypt

**Author’s Country/Territory:** India

**Manuscript submission date:** 2025-04-28

**Reviewer chosen by:** Hong-Xin Jiang

**Reviewer accepted review:** 2025-05-14 18:32

**Reviewer performed review:** 2025-05-20 15:34

**Review time:** 5 Days and 21 Hours

<b>Content to be reviewed</b>	<p>Does the manuscript’s content fall within the scope of the journal? <b>Yes</b></p> <p>Is there any Key Word that is not included in the manuscript title? <b>Yes</b></p> <p>Do authors’ affiliations correspond to the content of the manuscript? <b>Yes</b></p> <p>Does the Abstract contain the contents of each part of the manuscript (IMRaD)? <b>Yes</b></p> <p>Are the Key Words complete? <b>Yes</b></p> <p>Is the content of the Introduction adequate? <b>Yes</b></p>
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Is the content of the Materials and Methods complete?

**Not Applicable**

Is the description of the experiments clear and complete? **Not Applicable**

Are the experimental data presented in the manuscript's biostatistics content reliable? **Not Applicable**

Are the experimental data of the Results true and reliable? **Not Applicable**

Are the quality and resolution of the images up to standard? **Yes**

Do the selection and design of the figures and tables follow the principles of necessity and clarity? **Yes**

Is there any duplication between various parts of the manuscript and between the main text and the content presented in the figures and tables? **No**

Are the figures and tables numbered consecutively in the order in which they appear in the manuscript? **Yes**

Is the content of the Discussion reasonable? **Yes**

Is the Conclusion reasonable? **Yes**

Are all references necessary and reasonable? **Yes**

Do authors omit important references? **Yes**

Are all references related to the topic of the manuscript? **Yes**

Do authors only cite their own earlier publications? **No**

Is the manuscript's text correct, concise, and clear? **Yes**

Will the manuscript's content be of interest to readers? **Yes**

Are additional experiments needed for the study? **No**

Does the research scope comply with ethics? **Not**



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

### **SPECIFIC COMMENTS TO AUTHORS**

The manuscript provides a concise yet comprehensive overview of hepatic osteodystrophy (HO), a significant but underrecognized complication of chronic liver disease (CLD). It covers the epidemiology, pathogenesis, diagnosis, and management of HO, emphasizing its multifactorial nature and the need for targeted interventions. The review is well-structured, with clear sections and a logical flow, making it accessible to readers in hepatology and endocrinology. However, there are areas where clarity, precision, and additional details could enhance the manuscript's impact and scientific



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rigor. Below are specific comments and suggestions for improvement. In abstract section, clarify the statement “bisphosphonates are the most efficient drugs” by specifying their efficacy in increasing BMD or reducing fracture risk. Simplify complex sentences and define ambiguous terms. For instance, clarify what “liver-specific considerations” entail (e.g., unique risk factors or altered pharmacokinetics in CLD). The diagnosis section mentions the use of DXA and FRAX but does not address limitations specific to CLD patients, such as the impact of ascites on DXA accuracy . The management section relies heavily on bisphosphonates and mentions denosumab and raloxifene but provides limited data on their long-term efficacy or safety in CLD patients. The role of anabolic agents like teriparatide is mentioned briefly without sufficient context. The prevalence data are compelling, but the section could benefit from a table summarizing rates across different CLD etiologies (e.g., PBC, viral hepatitis, ALD). Consider adding a sentence on the economic or clinical burden of HO to underscore its importance. The screening recommendations (e.g., BMD every 1–2 years for PBC, 2–3 years for cirrhosis) are presented without referencing specific guidelines or consensus statements. Consider adding a table summarizing prevalence data or a flowchart for screening and management to enhance clinical utility. The reference list is robust, but some citations (e.g., Ref. 7, a 2025 study) are listed as “e-pub ahead of print” without full publication details, which may limit accessibility for readers. Elaborate on key mechanisms (e.g., how sclerostin inhibits Wnt/ $\beta$ -catenin signaling) and their relevance to bone loss in CLD. For genetic factors, clarify whether identified polymorphisms (e.g., VDR, COLIA1) are actionable in clinical practice or require further validation. Briefly address whether other emerging osteoporosis therapies have been studied in CLD or are under investigation, even if data are preliminary.



**RE-REVIEW REPORT OF REVISED MANUSCRIPT**

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**Manuscript NO:** 109093

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**Provenance and peer review:** Invited Manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer's code:** 08501193

**Position:** Peer Reviewer

**Academic degree and professional title:** MD, PhD

**Reviewer's Country/Territory:** China

**Author's Country/Territory:** India

**Manuscript submission date:** 2025-04-28

**Reviewer chosen by:** Huo Liu

**Reviewer accepted review:** 2025-06-18 15:04

**Reviewer performed review:** 2025-06-18 15:25

**Review time:** 1 Hour

<b>Content to be reviewed</b>	Does the manuscript's content fall within the scope of the journal? <b>Yes</b> Is there any Key Word that is not included in the manuscript title? <b>No</b> Do authors' affiliations correspond to the content of the manuscript? <b>Yes</b> Does the Abstract contain the contents of each part of the manuscript (IMRaD)? <b>Yes</b>
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Are the Key Words complete? **Yes**

Is the content of the Introduction adequate? **Yes**

Is the content of the Materials and Methods complete? **Not Applicable**

Is the description of the experiments clear and complete? **Not Applicable**

Are the experimental data presented in the manuscript's biostatistics content reliable? **Not Applicable**

Are the experimental data of the Results true and reliable? **Not Applicable**

Are the quality and resolution of the images up to standard? **Not Applicable**

Do the selection and design of the figures and tables follow the principles of necessity and clarity? **Yes**

Is there any duplication between various parts of the manuscript and between the main text and the content presented in the figures and tables? **No**

Are the figures and tables numbered consecutively in the order in which they appear in the manuscript? **Not Applicable**

Is the content of the Discussion reasonable? **Yes**

Is the Conclusion reasonable? **Yes**



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	<p>Are all references necessary and reasonable? <b>Yes</b></p> <p>Do authors omit important references? <b>No</b></p> <p>Are all references related to the topic of the manuscript? <b>Yes</b></p> <p>Do authors only cite their own earlier publications? <b>No</b></p> <p>Is the manuscript's text correct, concise, and clear? <b>Yes</b></p> <p>Are additional experiments needed for the study? <b>No</b></p> <p>Does the research scope comply with ethics? <b>Yes</b></p> <p>Will the manuscript's content be of interest to readers? <b>Yes</b></p>
<b>Scientific quality</b>	Grade B (Very good)
<b>Novelty of this manuscript</b>	Grade B (Very Good)
<b>Creativity or innovation of this manuscript</b>	Grade B (Very Good)
<b>Scientific significance of the conclusion in this manuscript</b>	Grade A (Excellent)
<b>Language quality</b>	Grade B (Very good)
<b>Does this manuscript describe a study of the existing knowledge system?</b>	No
<b>Does this manuscript report a</b>	No



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revolutionary innovation?	
Does this manuscript report an unconventional innovation?	No
Conclusion	Accept
Peer-reviewer statements	Peer-Review: Anonymous
	Conflicts-of-Interest: No

#### **SPECIFIC COMMENTS TO AUTHORS**

The authors have made good revisions. I recommend acceptance of this paper.