



**PEER-REVIEW REPORT**

**Name of journal:** *World Journal of Virology*

**Manuscript NO:** 113217

**Title:** Thrombotic Risk in Hepatitis C: Interplay Between Hepatic Dysfunction, Viral-Driven Inflammation, and Cardiovascular Consequences

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

**Peer-review model:** Single blind

**Reviewer’s code:** 07806810

**Position:** Peer Reviewer

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

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

**Author’s Country/Territory:** United States

**Manuscript submission date:** 2025-08-18

**Reviewer chosen by:** Jia-Lin Zhang

**Reviewer accepted review:** 2025-08-25 08:25

**Reviewer performed review:** 2025-08-25 08:36

**Review time:** 1 Hour

<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>No</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>
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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**

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? **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? **Not Applicable**



	Are the figures and tables numbered consecutively in the order in which they appear in the manuscript? <b>Yes</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 B (Very 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>	No
<b>Does this manuscript report an unconventional innovation?</b>	No
<b>Conclusion</b>	Minor revision
<b>Re-review</b>	No
<b>Peer-reviewer statements</b>	Peer-Review: Anonymous
	Conflicts-of-Interest: No
<b>Are your review comments generated by AI tools?</b>	No

## SPECIFIC COMMENTS TO AUTHORS

### Overall Significance and Contribution

The manuscript provides a timely and comprehensive overview of the prothrombotic state associated with chronic Hepatitis C virus (HCV) infection, effectively integrating hepatic, inflammatory, and cardiovascular perspectives. The emphasis on the shift from the traditional view of cirrhosis as an anticoagulated state to a fragile rebalanced



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hemostasis is particularly insightful. However, the review would benefit from a clearer articulation of its novel contributions relative to existing literature, especially given the increasing attention to extrahepatic manifestations of HCV.

#### Strength of Evidence and Literature Coverage

The authors have compiled a robust body of evidence from epidemiological, clinical, and mechanistic studies to support the association between HCV and thrombotic risk. The inclusion of recent studies on direct-acting antivirals (DAAs) and their impact on endothelial function and thrombotic events is a strength. That said, the review could be enhanced by more explicit discussion of the quality and levels of evidence (e.g., prospective vs. retrospective studies) and by addressing contradictory findings, such as those regarding viral load and disease severity.

#### Clarity and Integration of Figures

While the figures are referenced in the text, their content and key messages are not sufficiently explained or integrated into the narrative. For instance, Figure 1 is mentioned briefly without a detailed legend or interpretation. The authors should ensure that each figure is clearly described in the text and that its role in supporting the central arguments is explicitly stated.

#### Depth of Discussion on DAA Therapy and Residual Risk

The section on DAA therapy appropriately highlights improved endothelial function and reduced thrombotic risk post-SVR. However, the discussion on residual risk in patients with advanced fibrosis—despite viral clearance—could be expanded. Mechanisms underlying persistent prothrombotic tendencies (e.g., irreversible vascular damage, epigenetic changes, or persistent immune activation) warrant deeper exploration to guide future research and clinical management.

#### Unresolved Questions and Future Directions

The manuscript correctly identifies major research gaps, including the lack of



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HCV-specific thrombotic risk scores and the need for biomarker-guided strategies. However, the proposed directions could be more specific. For example, suggesting particular biomarkers (e.g., von Willebrand factor, D-dimer, or IL-6) for validation in prospective cohorts, or outlining design considerations for interventional trials (e.g., anticoagulation in DAA-treated vs. untreated patients), would strengthen this section.

#### Organization and Redundancy

The review is generally well-structured, but some topics—such as the description of coagulation imbalance in cirrhosis—are repeated across sections. Streamlining the discussion of pathophysiological mechanisms into a more cohesive narrative would improve readability and impact. Additionally, the conclusion could be more forward-looking, emphasizing clinical implications and actionable recommendations for hepatologists, cardiologists, and primary care providers.



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## PEER-REVIEW REPORT

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**Peer-review model:** Single blind

**Reviewer's code:** 08784640

**Position:** Peer Reviewer

**Academic degree and professional title:** MD

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

**Author's Country/Territory:** United States

**Manuscript submission date:** 2025-08-18

**Reviewer chosen by:** AI Editor

**Reviewer accepted review:** 2025-08-23 13:06

**Reviewer performed review:** 2025-08-29 12:18

**Review time:** 5 Days and 23 Hours

<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>Yes</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> Are the Key Words complete? <b>Yes</b>
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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 B (Very good)
Novelty of this manuscript	Grade C (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 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	Major revision
Re-review	Yes
Peer-reviewer statements	Peer-Review: Anonymous
	Conflicts-of-Interest: No
Are your review comments generated by AI tools?	No

**SPECIFIC COMMENTS TO AUTHORS**

Reviewer Report

Manuscript No: 113217

Title: Thrombotic Risk in Hepatitis C: Interplay Between Hepatic Dysfunction, Viral-Driven Inflammation, and Cardiovascular Consequences

Reviewer: Anonymous

Date: 29 August 2025

#### General Assessment

The manuscript provides a well-structured and informative review of the relationship between chronic hepatitis C virus (HCV) infection and cardiovascular disease (CVD). The authors synthesize epidemiological, pathophysiological, and clinical trial data effectively, offering a comprehensive perspective on the topic. The paper is timely, given the increasing recognition of extrahepatic manifestations of HCV and the evolving therapeutic landscape with direct-acting antivirals (DAAs).

Overall, the manuscript is clear, well-written, and relevant. However, several aspects require clarification and expansion to enhance its impact and value for the readership.

#### Major Points for Revision

##### 1. Epidemiology and Global Burden (Introduction)

The introduction would benefit from the inclusion of \*\*global epidemiological data, such as updated WHO estimates on HCV prevalence and the global burden of cardiovascular disease in this population. This will frame the clinical importance of the review more clearly.

##### 2. Pathophysiology Section

While comprehensive, there are redundancies across subsections (e.g., chronic inflammation discussed in both cryoglobulinemia and oxidative stress contexts). Consolidating overlapping material will improve clarity and flow.

Consider adding a brief comparative discussion of HCV-related mechanisms vs. traditional CVD risk factors (e.g., diabetes, dyslipidemia, hypertension) to highlight the unique contribution of HCV.

##### 3. Residual Cardiovascular Risk Post-DAA Therapy

The review mentions residual risk after viral eradication but should provide



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greater detail with specific data. Large cohort studies (e.g., VA cohorts, European multicenter studies) demonstrate that while DAA therapy reduces CVD incidence, risk remains elevated compared to uninfected populations. Referencing such data will strengthen this section (e.g. Backus et al., European HCV-HIV cohort)

#### 4. Biomarkers and Risk Stratification

The discussion of biomarkers and scoring systems for risk prediction is currently too general. Consider highlighting specific biomarkers that have been studied in this context (e.g., hs-CRP, IL-6, D-dimer, NT-proBNP) and how they might be integrated into clinical risk scores.

#### 5. Figures and Visuals

Figure 1 is informative but requires improved resolution and clarity. Labels should be enlarged, and pathways more distinctly illustrated for readability.

#### Minor Points for Revision

**References:** There appear to be some redundancies or overlapping references. A careful check to eliminate duplicates or near-duplicates will streamline the bibliography. There appear to be redundant references, particularly in sections discussing HCV-associated thrombosis and hemostasis in cirrhosis. Streamlining these would improve clarity. For example, Refs. 7, 9, and 10 all address HCV and thrombosis, and Refs. 12, 13, and 16 cover hemostasis in cirrhosis. Consider consolidating these.

**Terminology Consistency:** Ensure consistent use of terms such as "extrahepatic manifestations" vs. "systemic complications."

**Language and Style:** Minor grammatical and stylistic improvements would further improve readability.

#### Summary of Required Revisions

1. Add updated WHO and global burden data in the Introduction.
2. Reduce redundancy in the Pathophysiology section; add comparative discussion with



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classic CVD risk factors.

3. Expand the section on residual CVD risk after DAA therapy with specific large-cohort evidence.
4. Provide examples of candidate biomarkers for risk stratification and elaborate briefly on their potential clinical utility.
5. Improve quality and clarity of Figure 1.
6. Review references for duplication and maintain consistent terminology.

#### Overall Recommendation

The manuscript addresses an important and clinically relevant topic with solid foundations. With revisions to improve clarity, add depth in certain areas, and refine presentation, it will make a valuable contribution to the field.

Recommendation: Major Revision (primarily for content enrichment and streamlining, not for fundamental flaws).