

## **Reviewer 1**

### **Reviewer Comment**

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 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.

### **Author Response:**

Thank you for your comment, We have made changes to the introduction, incorporating your feedback.

### **Reviewer Comment**

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.

### **Author**

### **Response:**

Thank you for your thoughtful feedback. We have added explicit references to the types of studies cited (retrospective and prospective cohorts, meta-analyses, cross-sectional,

longitudinal, case-control, and comparative studies) to clarify levels of evidence. We also expanded the discussion of contradictory findings regarding viral load and disease severity, noting that while higher viral load may reflect infection severity, it does not consistently predict progression of hepatic dysfunction. Instead, factors such as age at infection, sex, alcohol use, and HBV/HIV coinfection likely play a larger role in HCV-related liver disease and hepatocellular carcinoma risk. This addition helps delineate that liver injury in HCV is more likely mediated by host immune responses than by viral replication alone.

### **Reviewer**

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.

### **Author Response:**

We appreciate this suggestion. We have expanded the text to more clearly describe the content and key messages of each figure and added detailed legends to improve interpretation. Figure 1, in particular, is now integrated into the narrative with explicit discussion of how it illustrates disparities in time to treatment and mortality, thereby reinforcing the study's central arguments.

### **Reviewer Comment**

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.

**Author**

**Response:**

Thank you for this helpful comment. We have expanded the discussion on residual thrombotic risk in patients with advanced fibrosis after viral clearance. The revised text now addresses persistent mechanisms including irreversible vascular injury, sustained low-level inflammation and immune imbalance, and enduring epigenetic changes such as DNA methylation and histone modifications. We also note that endothelial dysfunction and vascular remodeling may persist despite SVR, particularly in those with cirrhosis. Together, these mechanisms explain why patients with advanced fibrosis remain at an elevated, though reduced, risk of cardiovascular and thrombotic complications even after DAA therapy.

**Reviewer**

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

**Author**

**Response:**

We appreciate this suggestion and have expanded the section on future directions to provide greater specificity. We now propose that risk stratification tools for HCV should incorporate clinical, hemostatic, and inflammatory biomarkers such as factor VIII, protein C, von Willebrand factor, D-dimer, and IL-6. We also outline design considerations for prospective studies, including interventional trials comparing

anticoagulation strategies in DAA-treated versus untreated patients, with endpoints such as bleeding risk, thromboembolic events, and longitudinal changes in endothelial function.

### **Reviewer Comment**

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.

### **Author Response:**

We streamlined the manuscript by reducing redundant descriptions of coagulation imbalance in cirrhosis and consolidating them into a single cohesive section. In addition, the conclusion has been revised to be more forward-looking, with emphasis on clinical implications. We now highlight actionable recommendations for hepatologists, cardiologists, and primary care providers, including universal HCV screening, early initiation of DAA therapy, management of cardiovascular risk factors, and multidisciplinary collaboration to address extrahepatic manifestations and reduce thrombotic complications.

## **Reviewer 2**

### **Reviewer**

### **Comment**

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.

### **Author**

### **Response:**

We thank the reviewer for the positive feedback. In response to the suggestions, we reduced redundancy throughout the manuscript to improve clarity and expanded the discussion on the independence of viral load from disease severity, emphasizing the role of immune-mediated mechanisms in driving liver injury.

### **Reviewer**

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.

### **Author Response:**

We appreciate this suggestion. We have revised the introduction to include updated WHO estimates on global HCV prevalence and recent data on the increased cardiovascular burden in this population, thereby framing the clinical importance of the review more clearly.

## **Reviewer Comment**

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.

## **Author**

## **Response:**

We have consolidated overlapping material, reducing redundancy between the cryoglobulinemia and oxidative stress sections. In addition, we expanded the discussion to compare HCV-related mechanisms with traditional cardiovascular risk factors, emphasizing HCV's role as a modifiable, nontraditional risk factor that can potentiate thrombotic and cardiovascular risk even in the absence of classic comorbidities.

## **Reviewer Comment**

The review mentions residual risk after viral eradication but should provide 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).

## **Author Response:**

We thank the reviewer for this suggestion. We have expanded the section on residual risk by adding data from large cohort studies, highlighting that while DAA therapy reduces CVD incidence, patients with HCV—such as those in VA and European

multicenter cohorts—continue to face elevated risk compared with uninfected populations.

### **Reviewer Comment**

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.

#### **Author**

#### **Response:**

We appreciate this comment and have revised the manuscript to include specific biomarkers studied in HCV-related cardiovascular risk. We now discuss IL-6, TNF- $\alpha$ , and hs-CRP, noting the paradox of suppressed CRP synthesis despite elevated IL-6 levels in chronic HCV, as well as the potential role of these biomarkers—along with D-dimer and NT-proBNP—in future risk stratification tools.

#### **Reviewer**

#### **Comment**

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

#### **Author**

#### **Response:**

We appreciate this feedback. Figure 1 has been revised with improved resolution, larger labels, and clearer pathway illustrations to enhance readability and ensure the key mechanisms are easily interpretable.

### **Reviewer Comment**

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. Ensure consistent use of terms such as "extrahepatic manifestations" vs. "systemic complications."

Minor grammatical and stylistic improvements would further improve readability.

**Author**

**Response:**

We thank the reviewer for this observation. We have carefully reviewed the reference list and removed duplicate or overlapping citations in sections on HCV-associated thrombosis and hemostasis in cirrhosis. Terminology has been standardized, with consistent use of "extrahepatic manifestations." In addition, we corrected minor grammatical issues and refined wording throughout the manuscript to improve readability.