

Reviewer #1

It was very interesting to read the manuscript titled “Similarities, differences, and possible interactions between HEV and HCV: what is the relevance for research and clinical practice?”. It is a very well-written manuscript with plethora of knowledge and references despite the paucity of work on the subject. I have few comments on the manuscript written below.

The main point is that the authors need to revise the abbreviations and provide a list to avoid confusion.

Abbreviations have been revised and a list of them has been provided.

Page 3, line 21: HCV hepatites; change to HCV hepatitis

Changed.

Page 4: Moreover, since the main limitation of the epidemiological surveys conducted so far is that only antibody tests were used [19, 37], coinfections and the effect of both viruses on liver disease progression should be better evaluated using direct detection of HCV and HEV RNA by molecular assays. Authors should elaborate more on the different methods (kits) used for determination of HEV IgG and their limitations.

Diagnostic accuracy and discordance among different methods have been discussed as follows:

“Moreover, the main limitation of the epidemiological surveys conducted so far is that only antibody tests were used [19, 66]. Detection of anti-HEV immunoglobulins is related to specificity and sensitivity of commercial kits, among which discordant results were reported in the literature [67]. In 2016, Norder and coworkers [68] evaluated the performance of five commercial assays to determine IgM and IgG levels against HEV. IgM titer was detected by a sensitive HEV IgM/HEV IgG test after the onset of symptoms, providing concordant results in 99% samples from patients with suspected HEV infection. By contrast, recomWell™ HEV IgG/IgM (Mikrogen Diagnostik, Neuried, Germany) and DS-EIA-ANTI-HEV-G/M™ (DSI Srl, Milan, Italy) tests were found to be less specific. In conclusion, investigating the actual rate of coinfections and the effect of both viruses on liver disease progression would require more accurate serological assays and more studies using direct detection of HCV and HEV RNA by molecular tests.”

Page 7: HEV/HCV coinfection can worsen the prognosis of hepatic and extrahepatic diseases [2, 3].

Change to “can worsen”

Changed.

Page 8: Lastly, at molecular level, miRNAs play a pivotal role in the progression of liver diseases [59]. The roles of the microRNAs are still under study, but it was already speculated that miR-628-3p, miR-194, miR-151-3p, miR-512-3p, miR-335 and miR-590 are potentially involved in HCV/HEV coinfection [60]. microRNAs should be written in full at first mention, with abbreviation between brackets.

microRNAs has been written in full at first mention, with abbreviation between brackets.

Page 9: The HCV RFs have been reported in few cases around the world, thus pathogenesis and therapy efficacy are not well characterized. Two patients infected by RF 2b/1b achieved viral clearance with an interferon-free regimen [67]. In contrast, a patient infected by the same RF failed two different interferon-free regimens [68]. No previous mention of RF as an abbreviation.

Previous mention of RF as an abbreviation has been provided.

Reviewer #2

This review article is on a novel topic which is not dealt with in much detail. The manuscript does make an attempt to address most of the salient features of both viruses and highlight areas where they might overlap.

However the discussion on the speculative overlap between the two viruses and how they could be affecting each other is lacking. There has been proposed model or concept. Table 2 could do with more details.

We have elaborated more on the overlap between the two viruses by adding a specific paragraph and more updated references. To better organize the text, we have changed the position of some paragraph already present in the new section titled: "MAJOR CAUSES AND EFFECTS OF COINFECTIONS". Along the same line, Table 2 was improved with more details.

Science Editor

The manuscript discusses the similarities, differences and possible interactions between HEV and HCV. This topic is very interesting, and there are few relevant studies. The manuscript is well written and can be helpful for the readers to ameliorate the diagnostic and therapeutic approach for this scenario. Nevertheless, there are a number points that may deserve some revisions.

1. There is a problem with the format of the table. The author should use a three line table.

Formatting of the table has been corrected.

2. I would like to make a suggestion to the author. Would it be clearer if you could have a figure to compare the relevant performance and mechanism of the two viruses, as well as the performance and mechanism of the two viruses?

Given the complexity of this topic and the fact that most conclusions are still speculative, we have accepted your suggestion but rather than drawing in details the relevant performance and mechanisms of the two viruses, we have decided to represent the major causes and effects of coinfections (including major mechanisms) in a more schematic way (Figure #1) to drive attention to one of the main subject of our review as suggested by Reviewer #2.

Company EIC

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, 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.

Thank you for your judgment and kind assistance with this paper. In addition to the responses to the Reviewers provided above, please note that only the parts added to the previous version have been corrected and approved by the professional editing services. We did not sent to the editing services the parts of the text that were already checked or those which have been simply moved to the new section titled: "MAJOR CAUSES AND EFFECTS OF COINFECTIONS".