Reviewer A:  
Recommendation: Revisions Required  
  
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Reviewer's Assessment

* There are significant papers ignored in the Introduction.

We added several papers as references.

* The figures/tables are not well conceived. Their information cannot be understood.

We made changes to figure 1 (highlighting numbers of cases instead of percentages) and tables 3 (added duration of treatment). We integrated the tables better with the manuscript’s text.

* The conclusions are not sound or are not based on the actual findings of the paper.

We reformulated the conclusions to better convey our message.

* The paper does not clearly identify the implications for research or practice.

We expanded the discussions section to express more clearly the role of hepatitis E an emerging healthcare problem.

Comments for Authors and Editor------------------------------------------------------

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Reviewer B:  
Recommendation: Revisions Required  
  
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Reviewer's Assessment

* The Abstract is not structured.

We reformulated the abstract to be clearer on the main points.

* The materials and methods are not properly described, so that the reader could clearly understand what was done and on whom. The chapter should be written in a way that the research can be reproduced.

We reformulated the methods. We separated more clearly the parts of the study, we added more precise explanations on which parameters we included, and we made our definitions clearer.

* The results are not presented clearly, they should be more concise, and precise.

We reformulated the results sections to make main parts of the study clearer. We integrated the tables more with the text of the manuscript.

* The results are not analyzed appropriately in the Discussion section.

We reformulated the discussions section to better convey our message.

* The conclusions are not sound or are not based on the actual findings of the paper.

We reformulated the conclusions section to better convey our message.

* There are references inserted in the text that do not provide the information presented in the text.

We updated our bibliography.

* Please provide all abbreviations in full on first use.

We added a full list of all abbreviations and explanations in full at first use.

Comments for Authors and Editor

The manuscript presents potentially interesting data on viral hepatitis E and viral hepatitis A. It provides information on the increased number of hospitalized patients with hepatitis E (2018 and 2019 compared to 2017) in a teaching hospital of North-western Romania, comparing clinical and paraclinical parameters in hepatitis E and hepatitis A group patients. The study underlines the potential of severe forms and death in the hepatitis E group patients.

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**Major issues are underlined below:**

**Abstract**

* Page 1, line 9 and 10- Methods section should not include results (number of patients included)

We moved the number of cases to the results section.

* Page 1, line 12- please present the total number of patients with hepatitis A and  hepatitis E in the study interval.

We reformulated to better reflect the number of cases. During the study period, there were 48 cases of hepatitis E, all adults and 152 adult cases of hepatitis A, used as controls plus other 262 cases of hepatitis A younger than 18, who were not included as controls.

* Page 1, line 14- a milder course of hepatitis E can not be sustained as more severe forms (25% versus 3.3%) and a mortality of 6.25% versus zero were described in the hepatitis E group compared to the hepatitis A group.

We reformulated to clearly state that hepatitis E patients showed less modified **laboratory** parameters, **while** comorbidities, severe and fatal cases were also more likely in the hepatitis E group.

* Pg 1, line 20 –the conclusions are not in accordance with the results section

We completely reformulated the conclusion paragraph.

**Backgroud and Aims**

* Page 1, line 31- please give references.

We reformulated to include more detailed data on Romanian studies and we added the respective references.

* Page 2, line 19- the methodology of surveillance of hepatitis A in Romania (updated 10.07.2019 by the National institute of Health) includes also isolation at home, but imposes reporting of the case to the health authorities.

We reformulated to state that during the study period, all cases were isolated in a hospital capable of isolating and treating acute viral hepatitis. The CNSCBT methodology only provides a way to declare that a patient was isolated at home with no indication whether patients can or cannot be isolated at home.

* Page 2, line 20- please define “appropriate hospital”

We reformulated to state that during the study period, all cases were isolated in a hospital capable of isolating and treating acute viral hepatitis. The CNSCBT methodology only provides a way to declare that a patient was isolated at home with no indication whether patients can or cannot be isolated at home.

* Page 2, line 25- the study was retrospective, but not case-control

We reformulated the methods section to better reflect our study design.

* Page 2, line 28-  general information should be presented in backgroud section

We moved the relevant phrase to the background section.

* Page 2, line 34– please define appropriate supportive treatment with references

We detailed the supportive treatment which was used for all patients during the study period. Our hospital’s protocols was written according to Wendon 2017 but it was ultimately each doctor’s judgment according to each patient’s presentation and evolution that contributed to individual medical decisions. Being a retrospective study and not clinical trial, each patient’s treatment was out of our control.

* Page 2, line 35 – “general recommendations” - please give references

We detailed the supportive treatment which was used for all patients during the study period. Our hospital’s protocols was written according to Wendon 2017 but it was ultimately each doctor’s judgment according to each patient’s presentation and evolution that contributed to individual medical decisions. Being a retrospective study and not clinical trial, each patient’s treatment was out of our control.

* Page 2, line 35, 36, 37, 38- the definition for severe case of hepatitis E in not found in the guideline cited. Please give the correct reference for the definition.

We provided a clearer explanation to our definitions, for both severe hepatitis E and A case, as well as the need for additional treatment with ribavirin or plasma products, respectively. Our definitions were created according to both our hospital protocols and EASL guidelines. We emphasized the fact that we created the definitions.

* Page 2, line 39, 40- please give a reference for the definition of severe hepatitis A

We provided a clearer explanation to our definitions, for both severe hepatitis E and A case, as well as the need for additional treatment with ribavirin or plasma products, respectively. Our definitions were created according to both our hospital protocols and EASL guidelines. We emphasized the fact that we created the definitions.

* Page 2, line 44- please define laboratory parameters

We listed the laboratory parameters in a parenthesis.

* Page 2, line 45 – please be more specific on “patient’s presentation and evolution”. What do you mean by subjective parameters?

We reformulated the relevant paragraph. Subjective data was detailed.

* Page 3, line 1- if the study was retrospective from the electronic database how was the informed consent signed for the study?

We reformulated the paragraph to provide more precise information on what was consented to, as well as how consent was obtained.

**Results**

* Page 3, line 17- methods section din not present collecting data for the pediatric patients, the retrospective study included consecutive adult patients (>18 years old).

We reformulated the relevant methods section, figure 1 and manuscript text related to it in order to better express the inclusion procedure. We separated more clearly the main part of the study, performed only on adults and the context, which takes into account the maximal incidence of hepatitis A in children.

* Page 3, line 18, figure 1- collecting data for all viral hepatitis (viral hepatitis B, C) including  minor patients  was not presented in  methods section.

We reconstructed figure 1 and its caption to show the absolute number of cases instead of percentages. We emphasized the fact that figure 1 contains all acute viral hepatitis patients, of all ages and etiologies, not just those included in the main study. In the methods section, we mentioned how we used the information in figure 1 as a context for the main study.

* **Information on data that was not presented in data collection should not appear in results section**!

**We reformulated the methods section to be clearer.**

* Page 3, figure 1- the number of hepatitis E and hepatitis A in each year (2017, 2018, 2019) is not presented, only the percentage of un unknown total number of hepatitis A, B, C, E (as mentioned before not presented in the method section).

We reconstructed figure 1 and its caption to show the absolute number of cases instead of percentages. We emphasized the fact that figure 1 contains all acute viral hepatitis patients, of all ages and etiologies, not just those included in the main study. In the methods section, we mentioned how we used the information in figure 1 as a context for the main study.

* Page 3, line 19- data collected for transmission source was not mentioned in methods section. What data was collected from the electronic file, as we have a retrospective study?

Since alimentary habits were not consistently reported in electronic forms, we considered that this information was not reliable enough to be used for analysis.

* Page 3- Results section does not present number of severe forms in both groups, though in the results section from the abstract that information was presented.

We reformulated the relevant sections to state more clearly how we defined severe forms and how it relates to the need for additional treatment. We also added the numbers and percentages of patients with severe forms. Table 2 also contains unadjusted OR and OR adjusted for comorbidities with confidence intervals and p-values.

* Page 5, line 5- please present in methods section the chronic medical conditions recorded

We added / reformulated the relevant information in the methods section.

* Page 5, line 11- please provide information on duration of ribavirin treatment recommended

We added a new column in table 3 and relevant information in text about the duration of ribavirin treatment.

* Page 5, table 2- please provide information on etiology of chronic liver disease, liver cirrhosis, detail the neurologic disease

We added / reformulated the relevant information in the methods section.

* Page 6, table 3 – MELD- please provide abbreviation in full at first use, provide reference and include it in data collection from the methods section.

We added the relevant information.

* Page 6, table 3 – please provide reference for ribavirin therapy recommendation in extrahepatic neurological manifestations of hepatitis E

We reformulated to more clearly state that ribavirin was administered in accordance with our hospital protocol and EASL guidelines

* **Page 7 and 8 - line numbering missing**

**We added our own line numbering.**

**Discussion section**

* First paragraph :
  + “Unexpected high number of severe and/or lethal cases” not supported by comparison with publications or reports from previous years in the same region, in Romania or neighbouring countries.

We reformulated this section to better show how we found an increased number of cases during 2018 and 2019 compared to 2017 and how this increase is unexplained.

* + “Health care costs” were not analysed in the study.

We reformulated to better reflect our intention

* + One can not argue on increase number of patients compared to 2016 as no data on the number of cases in 2016  was provided (though it was mentioned that the same protocol for detection was used in 2016).

We reformulated this section to better show how we found an increased number of cases during 2018 and 2019 compared to 2017 and how this increase is unexplained.

* Second paragraph:
  + PCR-based genotyping assays- only PCR-based assays should be mentioned for diagnosis, genotyping is not necessary for diagnosis

We reformulated this paragraph. Diagnosis is generally performed using serological assays. In addition to diagnosis, PCR assays are used to measure viral load which is useful for follow-up in chronic cases and to genotype viral samples. In our sample, only diagnosis (using serological methods) was performed.

* + The same laboratory request form should be added

We reformulated to better show that patients were tested for acute viral hepatitis A, B, C and E with one request, at a clinical presentation suggestive for acute viral hepatitis

* 3rd paragraph:
  + “acute infection has a higher incidence in men” -the study shows a higher hospitalisation proportion of hepatitis E in men than women, as real incidence of the disease is still unknown.

We reformulated this section to state our intention more clearly.

* Page 8, 3rd paragraph- severe thrombocytopenia with contraindication to ribavirin was not presented in results section.

We added the relevant information.

* Page 8, 4th paragraph- severe hepatitis A, as mentioned before, not presented in results section.

We reformulated the results and methods sections to emphasize what severe cases mean for hepatitis A, the fact that severe hepatitis A cases received plasma products and how hepatitis E had a relatively higher proportion of severe cases (needing additional treatment).

* Page 8, 4th paragraph- as more patients with severe form (in number and percentage) and death are present in hepatitis E group compared to hepatitis A group, milder disease in hepatitis E can not be supported.

We reformulated the relevant sections in the methods, results and discussions chapters.

* Page 8, 5th paragraph- no presumption on genotyping can be made in the absence of laboratory data.

We reformulated to show that our presumption was based on other studies in the same geographic region that found that most cases were genotypes 3 and 4.

* Please compare the proportion of severe forms and mortality rate in your study with results of similar studies.

We reformulated the methods and discussions sections to emphasize how other studies also showed relatively high mortality in selected cases.

**Conclusions section**

* First line- compared to 2017, as no data on previous years is provided.
* Line 2- wrong conclusion – as presented before: as more patients with severe form (in number and percentage) and more death are present in hepatitis E group compared to hepatitis A group, milder disease in hepatitis E can not be supported.
* Line 3- the benefit of antiviral therapy should not be evaluated from retrospective studies
* **The conclusions should be reformulated**

 We reformulated the conclusions section.

**Minor issues**

* Page 2, line 17- EASL- please provide abbreviation in full at first use

We provided a list of abbreviations at the beginning and explanations at first use.

* Page 2, line 30- there is a grammar mistake: management of **the** patients

We reformulated the section.

* Page 3, footnote- please include it as reference at the end of the document

We provided a reference entry for the software.

* Page 5, line 17- spelling mistake- multiple system organ failure

We reformulated our phrasing.

* Page 7- HE- please provide abbreviation in full at first use

We used the full name (hepatitis E)

* 4th  paragraph of discussion section- there is a spelling mistake “sample” instead of study

We reformulated our phrasing.