

To the Editor in Chief of *World Journal of Gastroenterology*

We re-submit to your attention the paper: **“HBV/HDV epidemiology: changes over time and possible future influence of the SARS-COV-2 pandemic”**

We have modified our manuscript " according with the suggestions of the reviewers.

The following changes (shown underlined in the new manuscript) have been made:

Reviewer #1: First: This study proposed that HDV virus may exist along with HBV and due to existing SARS-CoV-2 pandemic diagnosis of HDV is under reported and this may lead to a catastrophic event caused due to hepatitis in near future. Therefore authors suggested to closely monitor the COVID-19 patient's serum anti-HDV during hospital admission with SARS-CoV-2 infection. Second: The quality is good however slight changes are suggested. This review showed the epidemiology of HDV in covid-19 patients and showed very few studies are actually reporting HDV in patients. Yes the conclusion was summarized appropriately. This study showed that the prevalence rate of HBV/HDV decreased in current population, but there could be rise in this rate if it remains unnoticed within population. The reasons why a hepatitis outbreak occurs are discussed along with the reasons why the numbers are reducing at present but why the numbers will again increase dramatically are also discussed very thoughtfully and provided several evidences. Third, the future directions of the topic described in this manuscript suggested that due to existing focus on COVID-19 the HDV prevalence rate may increase in global population. This study will impact the basic science as well as the clinical practice since it suggests the diagnosis of HDV infection in COVID-19 patients. The limitations, the questions/issues that remain to be solved are listed below;

Point 1. A comma was inadvertently placed after and kindly place it after cases “Peg-interferon alfa, the only recommended therapy, clears HDV in only 10-20% of cases and, consequently, new treatment strategies are being explored”.

Answer point 1: The observation of the reviewer has been accepted and the manuscript modified accordingly.

Point 2. First sentence of Introduction section, the word “liver-tropic” please mention as “liver tropic virus” remove the hyphen or else mention as “hepatotropic”.

Answer point 2: The observation of the reviewer has been accepted and the manuscript modified accordingly.

Point 3. “Chronic HDV infection is the most severe and rapidly progressive form of chronic hepatitis, leading to cirrhosis in 70% of patients in 5-10 years.” Please replace the “in 5-10 years” with “within”.

Answer point 3: The observation of the reviewer has been accepted and the manuscript modified accordingly.

Point 4. “Comparing HBV mono-infected patients with the HBV/HDV co-infected, the latter show a better outcome if reinfection is prevented by the continuous administration of nucleos(t)ide analogues and of hepatitis B immune globulins (HBIG)”. Please remove the second “of” not necessary.

Answer point 4: The observation of the reviewer has been accepted and the manuscript modified accordingly.

Point 5. “Further changes are expected in this era of the COVID-19 pandemic, which might involve, among others, a lower possibility of screening and access to treatment and a reduced effectiveness of the vaccination policy against HBV infection and of the management of patients with severe chronic hepatitis.” Please mention “for the management of patients with severe chronic hepatitis”.

Answer point 5: The observation of the reviewer has been accepted and the manuscript modified accordingly.

Point 6. “These epidemiological changes, of great impact on the health and quality of life of human beings, are the subject of this review”, please rewrite as “These epidemiological changes has great impact on the health quality of life of human beings, are the subject of this review”.

Answer point 6: The observation of the reviewer has been accepted and the manuscript modified accordingly.

Point 7. Some of the sub-headings are in caps while some are not, please maintain as per journal’s instruction.

Answer point 7: The observation of the reviewer has been accepted and the manuscript modified accordingly.

Point 8. Please correct the tense of this sentence “HDV is spread all over the world, with a global disease burden around 62-72 million HBV/HDV co-infected subjects”.

Answer point: The observation of the reviewer has been accepted and the manuscript modified accordingly.

Point 9. The country “French Guiana” is an old term or former name, please write it as French Guyana or mention formerly known as French Guiana.

Answer point 9: The observation of the reviewer has been accepted and the manuscript modified accordingly.

Point 10. “in Yucpa Indians in Venezuela” please rewrite as “Yucpa Indians of Venezuela” also “in 8 city hospitals in Mongolia” change to in 8 city hospitals of Mongolia.

Answer point 10: The observation of the reviewer has been accepted and the manuscript modified accordingly.

Point 11. Under the sub-headings in this sentence “To offer the readers an overview of the worldwide variability of the prevalence of anti-HDV among HBV chronic carriers, we report data recorded at different times in some countries”, please mention the year range in which the varying studies were performed across various geographical locations within bracket example (1977-2015).

Answer Point 11: The observation of the reviewer has been accepted and the manuscript modified accordingly.

Point 12. Please check the spacing between these two words “data recorded” of the above mentioned sentence.

Answer point 12: The observation of the reviewer has been accepted and the manuscript modified accordingly.

Point 13. Similar, to the addition done as per point 11 please do it for the next paragraph for low prevalence too.

Answer point 13: The observation of the reviewer has been accepted and the manuscript modified accordingly.

Point 14. Last sentence of page 12 it should be “patient’s fear”.

Answer point 14: The observation of the reviewer has been accepted and the manuscript modified accordingly.

Point 15. It is important to mention that HBV patients are at high risk of acquiring SARS-CoV-2 infection.

Answer point 15: The observation of the reviewer has been accepted and the manuscript modified accordingly.

Point 16. Under subheading “SARS-COV-2 PANDEMIC: REDUCED OPPORTUNITY FOR SCREENING, MANAGEMENT, AND TREATMENT” sixth sentence “Overall, all hepatology activities,” better to mention as “Overall, hepatological activities.

Answer point 16: The observation of the reviewer has been accepted and the manuscript modified accordingly.

Point 17. Please put the reference 29 in the last sentence of the paragraph.

Answer point 17: The observation of the reviewer has been accepted and the manuscript modified accordingly.

18. Page 12 “intra-family spread and men-who-have-sex-with men[44,50,67,93-95] ” better to mention the word “homosexual and heterosexual” as this will help to find the article more rapidly during Google search.

Answer point 18: The observation of the reviewer has been accepted and the manuscript modified accordingly.

Point 19. Please add the data for sex workers as well since very are vulnerable to viral hepatitis.

Answer point 19. The observation of the reviewer has been accepted and the manuscript modified accordingly.

Point 20. The epidemiological information given under subheading “HDV/HBV Chronic Infection” has to be segregated from the information given about the reasons for reduced prevalence rate. Please segregate and make two different paragraphs.

Answer point 20: The observation of the reviewer has been accepted and the manuscript modified accordingly.

Point 21. Point 21. It would be best if the epidemiological findings are segregated as per the decades irrespective of the countries where the studies were conducted and accordingly the sub-headings can be changed. If you are not willing to do so atleast align the sentence with epidemiological information in year wise chronological manner.

Answer point 21: According with the suggestion of the reviewer, the sentences reporting epidemiological information were aligned in year wise chronological manner, considering the year of the first observation.

Point 22. “The epidemiology of HDV infection has changed a lot in nearly every country since its first identification 55 years ago” Please add a citation for this and below it place the sentence “Outbreaks of fulminant hepatitis were first described in the Amazon Basin, in French Guiana, in Yucpa Indians in

Venezuela and in the Central African Republic[14-19]. Small but similar outbreaks have been observed also in northern Colombia and designated as hepatitis of Santa Marta (de sierra Nevada)[20-22]. Please add the year of occurrence for the respective regions. Earliest discovery of HDV in patients can be mentioned in a separate paragraph and can be added in the introduction section. Now if these studies [Reference 14-22] if they have found that acute liver failure in patients then what was the exact number of deaths please mention it.

Answer point 22: The observation of the reviewer has been accepted and the manuscript modified accordingly. However, with regard to the reviewer's request on the number of deaths it should be noted that it is not possible to calculate this numbers because most of the studies cited were performed on autopsy material collected decades before the discovery of HDV (this was disclosed in the new manuscript) and that the most recent studies were not structured to obtain this important datum.

Point 23. Better to merge the acute infections in geographic location [Reference 23-28] with hospitalized acute infection [Reference 29-32] into one example - Acute hepatitis cases, please choose a suitable sub-heading.

Answer point 23: The observation of the reviewer has been accepted and the manuscript modified accordingly.

Point 24. These sentences need citation and mention the year “In patients with fulminant hepatitis, morphologic studies showed marked liver steatosis with characteristic “morular hepatocytes”, cells with small droplets of fat and central pycnotic nuclei. Worthy of note, some similarities in the clinical presentation of fulminant hepatitis Delta with that of yellow fever has led to the hypothesis that some of the outbreaks occurring in the past in the Amazon basin and attributed to yellow fever, may have been due to HBV/HDV co-infection”.

Answer point 24: The observation of the reviewer has been accepted and the manuscript modified accordingly.

Point 25: Please refer if any research article showed superinfection of HBV/HDV, HIV and COVID-19 in a single patient.

Answer point 25: Considering the high number of subjects with triple HBV, HDV and HIV infections, it is highly likely that some of them contracted SARS-CoV-2 infection, asymptomatic or symptomatic. Even in the absence of data in the literature, I reported this possibility in the new manuscript.

Point 26: Reference [14] is incomplete I am unable to refer it in Google.

Answer point 26: The observation of the reviewer has been accepted and the manuscript modified accordingly.

Point 27. No need of this sentence please remove it “To provide readers with an organic view of the spread of HDV infection around the world over the past 5 decades, we will separately analyze published epidemiological data concerning both acute HDV infections, observed during outbreaks or in planned clinical studies, and chronic HDV infection and then make some conclusive remarks”.

Answer point 27: The observation of the reviewer has been accepted and the manuscript modified accordingly.

Point 28. Please mention the disease name as COVID-19 not just covid.

Answer point 28: The observation of the reviewer has been accepted and the manuscript modified accordingly.

Point 29. The occurrence of HDV and HIV super-infection in patients was not mentioned at all, it has to be mentioned. Please provide the epidemiological data relevant to it.

Answer point 29: The observation of the reviewer has been accepted and the manuscript modified accordingly.

Point 30. Often test with anti-HDV IgM, hepatitis D antigen (HDAg) or HDV RNA as an initial test are not considered accurate as these are inconsistently expressed markers of HDV infection. However, here it was not considered please explain.

Answer point 30: The observation of the reviewer has been accepted and the manuscript modified accordingly.

Reviewer #2: I have read the manuscript entitled HBV/HDV epidemiology: changes over time and possible future influence of the SARS-COV-2 pandemic, submitted to World Journal of Gastroenterology. In this paper, the authors aimed to review the epidemiological changes HBV/HDV and possible future influence on human beings during the COVID-19 pandemic. The article is presented in an intelligible fashion and written in standard English. I have no questions to ask.

No answer because no question from the reviewer

Reviewer #3: Do you think that if the incidence of COVID-19 decreases, the increase in the incidence of hepatitis will stop?

Answer: The observation of the reviewer has been accepted and this sentence has been included in the new manuscript: "When the COVID-19 emergency draws to a close, there will be a resumption of health activities for all diseases neglected during the pandemic, including screening for HBV and HDV infection and a false increase in the prevalence of these infections will occur; false because the effect of the recovery of undiagnosed cases in 2020, 2021 and, for some countries with reduced vaccination activity against COVID-19, even in some subsequent years."

Reviewer #4: This work is well done and should be accepted for publication

No answer because no question from the reviewer

Reviewer #5: According to my knowledge, it is a novel paper in its field opening new horizons for further evidence. In addition, the object as well as the results are appropriately discussed in the context of previous literature explaining the importance of the manuscript in its field. Authors succeed to present their data in a clear way adding information to the existing literature. Therefore, I have no corrections or further work to propose for the improvement of the manuscript and therefore it can be published unaltered.

No answer because no question from the reviewer

We thank the Editor and the Reviewers for helping us to improve our paper.

The manuscript has been read and approved by all the authors and has not been submitted for publication to other journals. We also declare that we have no conflict of interest in connection with this paper. Neither the manuscript nor part of it has been published or is under consideration for publication elsewhere.

We sincerely hope that the enclosed manuscript can be accepted for publication in the "*World Journal of Gastroenterology*".

Sincerely yours
Prof. Evangelista Sagnelli