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Letter to Editor

The Complex Interplay of Hepatitis D in Patients with Hepatitis B: Letter to the Editor

Dear Editor

I read with great interest the article by Safarpour and colleagues on the epidemiology of hepatitis D virus (HDV) and its associated factors in southern Iran. The authors reported that, of 137 patients with chronic hepatitis B, 21.2% (n=29) tested positive for HDV using a competitive enzyme immunoassay (ELISA) kit, with a reported sensitivity and specificity of approximately 90% and 100%, respectively.[1]

It is important to note that this study included only patients with low hepatitis B virus (HBV) DNA levels. Although HDV infection typically suppresses HBV replication, this is not universal; up to 19.3% of patients could have HBV DNA levels exceeding 10,000 IU/mL by four logs.[2] The viral kinetics of HBV and HDV coinfection could be categorized into three profiles: HDV-dominant (low HBV DNA), HBV-dominant (high HBV DNA), and profiles with equivalent levels of both viruses.[2] Furthermore, HBV genotype D, the most prevalent genotype in Iran, might co-infect with HDV, leading to higher HBV DNA levels.[2]

This study design has limited power to detect HBV/HDV coinfection compared to HDV superinfection. Many guidelines recommend screening all HBsAg-positive individuals for HDV using reliable serological tests, irrespective of HBV DNA level.[3] This limitation raises concerns about the accuracy of the reported HDV prevalence among the HBV-infected patients in this study.

The effect of age on acquiring HDV infection has been described in many reports. Interestingly, in this series, a history of dental procedures was reported as protective. This finding might be a proxy for greater health awareness and better access to healthcare among those without HDV infection. Therefore, it should be interpreted with caution.

Additionally, the study did not report on coinfection with other viruses, such as the hepatitis C virus (HCV) and human immunodeficiency virus (HIV), which are known to increase the risk of HDV acquisition. For example, a study from Shiraz, Iran, demonstrated a higher prevalence of HDV among HIV/HBV-coinfected patients.[4]

In conclusion, this report highlighted the need for more comprehensive and accurately designed studies to assess the true prevalence and impact of HDV infection in Iran.

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Keywords ● Hepatitis B virus ● Hepatitis D virus ● Epidemiology ● Iran

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References

1 Safarpour AR, Shahedi A, Fattahi MR, Sadeghi E, Akbarzadeh M, Ahmadi L, et al. Epidemiology of Hepatitis D Virus and Associated Factors in Patients Referred to Level Three Hepatitis Clinic, Fars Province, Southern Iran. Iran J Med Sci. 2025;50:220-8. doi: 10.30476/ijms.2024.101949.3469. PubMed PMID: 40255222; PubMed Central PMCID: PMCPMC12008655.
2 Sausen DG, Shechter O, Bietsch W, Shi Z, Miller SM, Gallo ES, et al. Hepatitis B and Hepatitis D Viruses: A Comprehensive Update with an Immunological Focus. Int J Mol Sci. 2022;23. doi: 10.3390/ijms232415973. PubMed PMID: 36555623; PubMed Central PMCID: PMCPMC9781095.
3 European Association for the Study of the L. EASL Clinical Practice Guidelines on hepatitis delta virus. J Hepatol. 2023;79:433-60. doi: 10.1016/j.jhep.2023.05.001. PubMed PMID: 37364791.
4 Motamedifar MP, Taheri MM, Lankarani KBM, Gholami MB, Lari MAM, Faramarzi HM, et al. The Prevalence and Risk Factors of Hepatitis Delta Virus in HIV/HBV Co-Infected Patients in Shiraz, Iran, 2012. Iran J Med Sci. 2015;40:448-53. PubMed PMID: 26379352; PubMed Central PMCID: PMCPMC4567605.

The Authors' Reply

Dear Editor

We sincerely thank the author of the letter for their meticulous review and interest in our article, "Epidemiology of Hepatitis D Virus and Associated Factors in Patients Referred to a Level Three Hepatitis Clinic, Fars Province, Southern Iran".[1] Their constructive comments provided a valuable opportunity to clarify the methodological and interpretive aspects of our study.

Regarding the High Prevalence of Hepatitis D Virus (HDV) and Patient Selection

We concur that the 21.2% HDV prevalence we reported is not representative of the entire population of hepatitis B virus (HBV) carriers.[1] Our sample selection was a deliberate clinical decision to investigate a specific dilemma: patients with a low HBV DNA load but elevated liver enzymes, a profile that often indicates HDV superinfection.

Furthermore, our focus on patients with elevated liver enzymes is supported by major clinical guidelines. For instance, the European Association for the Study of the Liver (EASL) emphasizes testing for HDV in HBsAg-positive individuals, particularly those with biochemical evidence of active liver disease, to explain ongoing inflammation and guide management.[2] Additionally, a global meta-analysis indicated higher HDV prevalence in specific clinical subgroups, such as those with chronic liver disease, which aligned with our patient selection.[3] This targeted screening strategy identified patients most at high risk for HDV superinfection and avoided unnecessary laboratory costs for the wider HBV-positive population.

Regarding the Protective Role of Dental Procedures

We agree with the author's interpretation regarding the potential role of confounding factors such as socioeconomic status (SES) and health awareness. Given the significant improvements in infection control standards in recent decades, dental procedures are no longer considered the risk factor they once were.[4] Therefore, regular dental visits can be an indicator of higher health literacy and better access to healthcare, which are associated with a lower risk of infection.[5]

Regarding Limitations and Co-infections

We sincerely appreciate the respected author's observation on the omission of data on co-infections with the hepatitis C virus (HCV) and human immunodeficiency virus (HIV), which is indeed a valid point. In our study, all patients were screened for both HCV and HIV, and none tested positive. As the result was uniformly negative, we did not include this data in the manuscript. Nevertheless, the suggestion to explicitly report such findings is well taken, as the absence of co-infection is itself an informative result.

We also acknowledge that the small number of HDV-positive cases (n=29) limited the statistical power to explore associations with other potential risk factors. This limitation is common in studies of rare diseases, where a low event frequency can hinder the identification of significant correlations.

In conclusion, we thank the respected author for this constructive scientific dialogue. We believe that our study, by highlighting HDV in a specific clinical context, underscores the need for more extensive research. This finding aligns with the global consensus that significant unmet needs remain in the diagnosis and management of hepatitis D, a point on which we and the author agree.

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References

1 Safarpour AR, Shahedi A, Fattahi MR, Sadeghi E, Akbarzadeh M, Ahmadi L, et al. Epidemiology of Hepatitis D Virus and Associated Factors in Patients Referred to Level Three Hepatitis Clinic, Fars Province, Southern Iran. Iran J Med Sci. 2025;50:220-8. doi: 10.30476/ijms.2024.101949.3469. PubMed PMID: 40255222; PubMed Central PMCID: PMCPMC12008655.

2 European Association for the Study of the L. EASL Clinical Practice Guidelines on hepatitis delta virus. J Hepatol. 2023;79:433-60. doi: 10.1016/j.jhep.2023.05.001. PubMed PMID: 37364791.

3 Stockdale AJ, Kreuels B, Henrion MYR, Giorgi E, Kyomuhangi I, de Martel C, et al. The global prevalence of hepatitis D virus infection: Systematic review and meta-analysis. J Hepatol. 2020;73:523-32. doi: 10.1016/j.jhep.2020.04.008. PubMed PMID: 32335166; PubMed Central PMCID: PMCPMC7438974.

4 Cleveland JL, Gray SK, Harte JA, Robison VA, Moorman AC, Gooch BF. Transmission of blood-borne pathogens in US dental health care settings: 2016 update. J Am Dent Assoc. 2016;147:729-38. doi: 10.1016/j.adaj.2016.03.020. PubMed PMID: 27233680; PubMed Central PMCID: PMCPMC5084444.

5 Patrick DL, Lee RS, Nucci M, Grembowski D, Jolles CZ, Milgrom P. Reducing oral health disparities: a focus on social and cultural determinants. BMC Oral Health. 2006;6:S4. doi: 10.1186/1472-6831-6-S1-S4. PubMed PMID: 16934121; PubMed Central PMCID: PMCPMC2147600.