

The Challenge of Hepatitis D Virus Coinfection in Iran: Age, Access, and Unanswered Public Health Questions

Dear Editor

I read with great interest the article by Safarpour and others,¹ entitled "Epidemiology of Hepatitis D Virus and Associated Factors in Patients Referred to Level Three Hepatitis Clinic, Fars Province, Southern Iran". This study addressed an important, yet often under-researched, area of viral hepatitis epidemiology, with its specific focus on hepatitis D virus (HDV) coinfection among hepatitis B virus (HBV) carriers in a specific region of Iran. I commend the authors for undertaking this prospective cohort analysis, which provided valuable regional data on HDV prevalence and its associated factors. While the study offered important insights, several aspects, particularly regarding the interpretation of prevalence estimates and the risk factor analysis, warrant further discussion from a public health perspective.

The authors reported an HDV positivity rate of 21.2% (29 out of 137) among the screened HBV patients.¹ This prevalence was notably high compared to estimates from some other regions of Iran mentioned in the introduction,^{2,3} and significantly higher than the estimated global average among HBV carriers.⁴ However, it is crucial to contextualize this finding within the study's specific sampling frame. Participants were selected from a referral clinic population based on specific clinical criteria, namely a low HBV viral load and elevated liver enzymes. This specific clinical profile might inherently select for patients with more frequent HDV superinfection. Therefore, while accurately reflecting the prevalence within this specific clinical subgroup, the 21.2% figure should be interpreted with caution and likely could not represent the general prevalence of HDV among all HBV carriers in Fars Province. This distinction is vital for accurately assessing the population-level disease burden and planning public health screening strategies.

The multivariate analysis identified increasing age as a significant risk factor for HDV infection, which aligned with findings from several other studies.⁵ From a public health perspective, this suggested a potential cumulative exposure risk over time or could reflect cohort effects related to past transmission dynamics or vaccination campaigns.¹ This finding reinforced the need for continued vigilance and possibly for targeted screening or counseling for older individuals with HBV infection.

Intriguingly, the study identified a history of dental procedures as a significant protective factor, a finding that appeared counterintuitive, as such procedures were often cited as a risk factor.⁵ The authors plausibly hypothesized that individuals accessing dental care might possess higher socioeconomic status (SES) or greater health awareness, factors associated with better overall health practices and a potentially lower risk of HDV. This interpretation highlighted a critical challenge in epidemiological studies: disentangling direct procedural risks from the broader social and behavioral determinants of health associated with healthcare utilization. Public health interventions might need to focus less on dental visits themselves and more on reaching populations with lower SES and health literacy.

Furthermore, the multivariate model failed to confirm a statistically significant association for several established HDV risk factors, including intravenous drug use or multiple sexual partners.¹ While this could reflect true differences in transmission dynamics, it is highly likely that it is influenced by the study's primary limitation: the small number of HDV-positive cases (n=29). This low number severely restricted the statistical power to detect such associations. Furthermore, the reliance on self-reporting for sensitive behaviors was prone to underreporting bias. Public health messaging must continue to emphasize known transmission routes, even if they were not statistically significant in this particular analysis. Finally, the study's single-center design also restricted the generalizability of its findings.

To advance our understanding of HDV epidemiology in Iran and inform effective public health strategies, future research should prioritize several avenues. First, population-based prevalence studies using random

sampling across diverse regions and settings are required to obtain more representative estimates. Second, larger cohort studies are essential to enhance statistical power for robust risk factor analysis, including the assessment of dose-response relationships. Third, studies incorporating detailed SES indicators are crucial to better explore the hypothesis that SES-associated factors mediate observed associations, such as the one with dental visits. Finally, qualitative research could provide deeper insights into local risk behaviors, knowledge gaps, and barriers to prevention and care related to HBV/HDV transmission.

In conclusion, Safarpour and colleagues provided important, hypothesis-generating data on HDV in a specific clinical cohort in southern Iran.¹ The high prevalence observed underscored HDV as a significant co-pathogen in certain patient groups with HBV, and the association with age was a key finding. However, the protective association with dental visits required careful consideration of underlying confounders, and the null findings for established risk factors were likely constrained by statistical power. This study effectively highlighted the need for broader, more robust epidemiological research to guide targeted screening, prevention, and control efforts for HDV within Iran.

Conflict of Interest: None declared.

Keywords • Hepatitis D virus • Hepatitis B virus • Co-infection • Public Health

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The Authors' Reply

Dear Editor

We would like to address the letter critiquing our article entitled “Epidemiology of Hepatitis D Virus and Associated Factors in Patients Referred to Level Three Hepatitis Clinic, Fars Province, Southern Iran”, which was published in the IJMS journal (Vol. 50, No. 4, April 2025).¹ Their constructive comments, including the affirmation of our key findings, such as the association of infection with increasing age, and their insightful analysis of other results, provided a valuable opportunity to further clarify the methodological and interpretive aspects of our study.

We respond to the key points raised in their letter as follows:

Regarding the High Prevalence of Hepatitis D Virus (HDV) in the Study Population

We concur with the esteemed author of the letter that the 21.2% hepatitis D virus (HDV) prevalence reported in our study appeared high at first glance.¹ As they astutely pointed out, this figure is not representative of the general population of hepatitis B carriers in Fars Province. Our sample selection was a deliberate clinical decision. As stated in our study, we selected patients for HDV testing who had elevated liver enzymes, alanine aminotransferase (ALT), despite a low hepatitis B virus (HBV) DNA load. This specific clinical profile is often indicative of HDV superinfection, which can lead to severe liver damage despite low HBV replication.² This targeted screening strategy, while effective for identifying high-risk patients, avoids imposing additional laboratory costs on the entire population of patients with HBV. Accordingly, the clinical practice guidelines of the American Association for the Study of Liver Diseases (AASLD) strongly recommend that all HBsAg-positive individuals be tested for HDV infection, particularly those with biochemical evidence of liver disease (e.g., elevated ALT).³

Regarding the Protective Role of Dental Procedures

We initially found the apparently protective association between a history of dental procedures and HDV infection to be counterintuitive and surprising. We concur with the authors that confounding factors, notably socioeconomic status (SES) and health awareness, are the most plausible explanation for this finding. We believe that this association could be attributable to these socioeconomic and behavioral factors within our study population, rather than a direct effect of the dental procedures themselves.

In recent years, the widespread implementation of universal precautions and significant improvement in infection control in dental centers have substantially reduced the risk of HBV and HDV transmission.⁴ Consequently, unlike in the past when dental procedures were considered a risk factor, regular dental visits might now serve as an indicator of better health status, greater awareness, and more effective access to health services.

To further explore this hypothesis, we reviewed the epidemiological literature. Several studies from Iran,⁵ Brazil,⁶ China, India, and Ghana⁷ have consistently indicated that individuals with lower socioeconomic status utilized dental services significantly less frequently. Furthermore, an extensive study of over 40,000 Iranian households showed that lower educational levels were associated with reduced dental check-ups,⁸ which could reflect lower health literacy in these populations.

Regarding the Lack of a Statistical Association between High-Risk Behaviors and HDV Transmission

We thank the author for these highly relevant points, which address key limitations that we acknowledged in our original manuscript. As correctly noted, the absence of statistically significant associations for several established HDV risk factors was a critical finding, which we believed was heavily influenced by the main limitation of our study, namely the small number of HDV-positive cases (n=29). As explicitly stated in our article, “the rarity of the disease limited the number of cases available for analysis, and this small sample size resulted in most factors not being significant in the initial analysis”.¹

We also highlighted that “the rarity of this disease limited the number of cases available for analysis.”¹ Furthermore, we concur with the author’s observation regarding potential underreporting of sensitive behaviors and the limited generalizability resulting from the single-center design of our study, which was explicitly detailed in our manuscript. Nevertheless, the principal goal of our research was to offer the first prospective epidemiological data on HDV in a region where information is scarce. Thus, our findings offered a crucial, albeit preliminary, foundation for future research. We strongly support the continued emphasis on all established HDV transmission routes in public health communications.

In conclusion, we are grateful to the author for his insightful analysis, which has fostered a constructive scientific dialogue. We agree that while our study highlighted the importance of HDV in the region, it also underscored the critical need for larger, more robust research along the pathways the author has indicated. We hope this exchange stimulates further advancement in the field.

Conflict of Interest: None declared.

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