

World Journal of *Hepatology*

World J Hepatol 2024 March 27; 16(3): 300-489



EDITORIAL

- 300 Is there a need for universal double reflex testing of HBsAg-positive individuals for hepatitis D infection?
Abbas Z, Abbas M

REVIEW

- 304 Non-alcoholic fatty liver disease and sleep disorders
Bu LF, Xiong CY, Zhong JY, Xiong Y, Li DM, Hong FF, Yang SL
- 316 Amebic liver abscess: An update
Kumar R, Patel R, Priyadarshi RN, Narayan R, Maji T, Anand U, Soni JR

MINIREVIEWS

- 331 Advances in discovery of novel investigational agents for functional cure of chronic hepatitis B: A comprehensive review of phases II and III therapeutic agents
Lam R, Lim JK
- 344 Protein succinylation, hepatic metabolism, and liver diseases
Liu S, Li R, Sun YW, Lin H, Li HF
- 353 Hepatocellular carcinoma immune microenvironment and check point inhibitors-current status
Gupta T, Jarpula NS

ORIGINAL ARTICLE

Case Control Study

- 366 Associations of PNPLA3 and LEP genetic polymorphisms with metabolic-associated fatty liver disease in Thai people living with human immunodeficiency virus
Choochuay K, Kunhapan P, Puangpetch A, Tongsima S, Srisawasdi P, Sobhonslidsuk A, Sungkanuparph S, Biswas M, Sukasem C

Retrospective Cohort Study

- 379 Comparison of fungal *vs* bacterial infections in the medical intensive liver unit: Cause or corollary for high mortality?
Khan S, Hong H, Bass S, Wang Y, Wang XF, Sims OT, Koval CE, Kapoor A, Lindenmeyer CC
- 393 Lean body mass index is a marker of advanced tumor features in patients with hepatocellular carcinoma
deLemos AS, Zhao J, Patel M, Kookan B, Mathur K, Nguyen HM, Mazhar A, McCarter M, Burney H, Kettler C, Chalasani N, Gawrieh S

Retrospective Study

- 405 Prediction model for hepatitis B e antigen seroconversion in chronic hepatitis B with peginterferon-alfa treated based on a response-guided therapy strategy
Zhang PX, Zheng XW, Zhang YF, Ye J, Li W, Tang QQ, Zhu J, Zou GZ, Zhang ZH
- 418 Retrospective study of the incidence, risk factors, treatment outcomes of bacterial infections at uncommon sites in cirrhotic patients
Schneitler S, Schneider C, Casper M, Lammert F, Krawczyk M, Becker SL, Reichert MC

Observational Study

- 428 Palliative long-term abdominal drains *vs* large volume paracenteses for the management of refractory ascites in end-stage liver disease
Kaur S, Motta RV, Chapman B, Wharton V, Collier JD, Saffioti F

Basic Study

- 439 Comprehensive prognostic and immune analysis of sterol O-acyltransferase 1 in patients with hepatocellular carcinoma
Gan CJ, Zheng Y, Yang B, Cao LM

SYSTEMATIC REVIEWS

- 452 Update in lean metabolic dysfunction-associated steatotic liver disease
Sato-Espinoza K, Chotiprasidhi P, Huaman MR, Díaz-Ferrer J

META-ANALYSIS

- 465 Influence of nonalcoholic fatty liver disease on response to antiviral treatment in patients with chronic hepatitis B: A meta-analysis
Liu SY, Wang D, Liu J, Yang LP, Chen GY
- 477 Prognostic value of neutrophil-to-lymphocyte ratio in end-stage liver disease: A meta-analysis
Cai XH, Tang YM, Chen SR, Pang JH, Chong YT, Cao H, Li XH

ABOUT COVER

Editorial Board Member of *World Journal of Hepatology*, Marcello Maida, MD, Doctor, Gastroenterology and Endoscopy Unit, S.Elia - Raimondi Hospital, Caltanissetta, Caltanissetta 93100, Italy. marcello.maida@hotmail.it

AIMS AND SCOPE

The primary aim of *World Journal of Hepatology* (*WJH*, *World J Hepatol*) is to provide scholars and readers from various fields of hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJH mainly publishes articles reporting research results and findings obtained in the field of hepatology and covering a wide range of topics including chronic cholestatic liver diseases, cirrhosis and its complications, clinical alcoholic liver disease, drug induced liver disease autoimmune, fatty liver disease, genetic and pediatric liver diseases, hepatocellular carcinoma, hepatic stellate cells and fibrosis, liver immunology, liver regeneration, hepatic surgery, liver transplantation, biliary tract pathophysiology, non-invasive markers of liver fibrosis, viral hepatitis.

INDEXING/ABSTRACTING

The *WJH* is now abstracted and indexed in PubMed, PubMed Central, Emerging Sources Citation Index (ESCI), Scopus, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 Edition of Journal Citation Reports® cites the 2022 impact factor (IF) for *WJH* as 2.4.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Yi-Xuan Cai, Production Department Director: Xiang Li, Cover Editor: Xiang Li.

NAME OF JOURNAL

World Journal of Hepatology

ISSN

ISSN 1948-5182 (online)

LAUNCH DATE

October 31, 2009

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Nikolaos Pyrsopoulos, Ke-Qin Hu, Koo Jeong Kang

EXECUTIVE ASSOCIATE EDITORS-IN-CHIEF

Shuang-Suo Dang

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/1948-5182/editorialboard.htm>

PUBLICATION DATE

March 27, 2024

COPYRIGHT

© 2024 Baishideng Publishing Group Inc

PUBLISHING PARTNER

Department of Infectious Diseases, the Second Affiliated Hospital of Xi'an Jiaotong University

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

POLICY OF CO-AUTHORS

<https://www.wjgnet.com/bpg/GerInfo/310>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

PUBLISHING PARTNER's OFFICIAL WEBSITE

http://2yuan.xjtu.edu.cn/Html/Departments/Main/Index_21148.html

Is there a need for universal double reflex testing of HBsAg-positive individuals for hepatitis D infection?

Zaigham Abbas, Minaam Abbas

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Liu D, China; Tavan H, Iran

Received: December 3, 2023

Peer-review started: December 3, 2023

First decision: January 15, 2024

Revised: January 16, 2024

Accepted: February 22, 2024

Article in press: February 22, 2024

Published online: March 27, 2024



Zaigham Abbas, Department of Hepatogastroenterology and Liver Transplantation, Dr. Ziauddin University Hospital, Karachi 75600, Sindh, Pakistan

Minaam Abbas, Department of Medicine, University of Cambridge, Cambridge CB2 0SP, United Kingdom

Corresponding author: Zaigham Abbas, AGAF, FACG, FACP, FCPS, FRCP, FRCPE, Professor, Department of Hepatogastroenterology and Liver Transplantation, Dr. Ziauddin University Hospital, Clifton, Karachi 75600, Sindh, Pakistan. drzabbas@gmail.com

Abstract

Hepatitis D virus (HDV) can infect HBsAg-positive individuals, causing rapid fibrosis progression, early decompensation, increased hepatocellular carcinoma risk, and higher mortality than hepatitis B virus (HBV) mono-infection. Most countries lack high-quality HDV prevalence data, and the collection techniques employed often bias published data. In recent meta-analyses, HDV prevalence in HBsAg-positive patients reaches 5%-15% and is even significantly higher in endemic areas. Since HBV vaccination programs were implemented, HDV prevalence has decreased among younger populations. However, owing to immigrant influx, it has increased in some Western countries. The current practice of HDV screening in HBsAg-positive individuals is stepwise, based on physician's discretion, and limited to at-risk populations and may require numerous visits. Double reflex testing, which includes anti-HDV testing in all HBsAg-positive individuals and then HDV RNA testing for anti-HDV-positive ones, is uncommon. Reflex testing can identify more HDV infection cases and link identified patients to further care and follow-up. Moreover, laboratory-based double reflex screening is less biased than physician-led testing. Therefore, health-care providers should learn about reflex testing, and federal and provincial hepatitis control programs should implement laboratory-based double reflex testing to obtain reliable HDV prevalence estimates. The test's cost-effectiveness depends on the number of HBV-positive patients screened to identify one HDV-positive patient. Such testing may be viable in areas with low HBsAg but high HDV prevalence. However, its economic impact on areas with low HDV prevalence needs further study.

Key Words: Anti-hepatitis D virus antibody; HBsAg; Hepatitis D virus RNA; Hepatitis B; Hepatitis D; Reflex testing

Core Tip: Most countries lack high-quality hepatitis D virus (HDV) prevalence data, and published data are often biased by the collection techniques employed. Currently, HDV diagnosis practice is stepwise. It relies on physician's discretion and requires numerous visits. Generally, only HBsAg-positive patients highly at risk for HDV are screened. Double reflex testing involves anti-HDV testing of all HBsAg-positive individuals, followed by HDV RNA testing for those who test positive for anti-HDV. This test approach is gaining attention because of the severe implications of HDV coinfection, and emerging as an effective strategy for identifying undiagnosed cases.

Citation: Abbas Z, Abbas M. Is there a need for universal double reflex testing of HBsAg-positive individuals for hepatitis D infection? *World J Hepatol* 2024; 16(3): 300-303

URL: <https://www.wjgnet.com/1948-5182/full/v16/i3/300.htm>

DOI: <https://dx.doi.org/10.4254/wjh.v16.i3.300>

INTRODUCTION

Hepatitis D significantly increases the risk of rapid fibrosis progression, early decompensation, hepatocellular carcinoma, and higher mortality than HBV mono-infection[1]. Most countries have no quality prevalence data, and published data are often biased. Meta-analyses indicate that 5%-15% of HBsAg-positive patients have been exposed to hepatitis D virus (HDV), accounting for 12-70 million individuals[2-4]. However, these meta-analyses focused on regions or pockets with a high infection probability. Recently, the adjusted HDV prevalence was lower in most countries and territories than previously reported[5]. In addition, many countries have no nationwide reports of HDV prevalence. The study (crude) prevalence of hepatitis D is not the same as the country prevalence because only those suspected to harbor HBV are tested and reported. Therefore, the reported HDV pockets do not represent country prevalence.

Since hepatitis B vaccination programs were implemented, the epidemiological landscape of hepatitis D has changed. In 2021, the global HDV prevalence was approximately at 262240000 and only a fraction of these infections were newly diagnosed[6]. However, the true prevalence of HDV remains uncertain because of the lack of awareness, limited access to reliable diagnostic tests for HDV antibody and HDV RNA, and high screening cost, resulting in the diagnosis of only 20%-50% of the true population infected with the HDV[1]. Most of the diagnosed population comprises immigrants and refugees in the West and residents of several Asian nations[7]. Although the HDV prevalence is generally decreased in the younger population resulting from robust HBV vaccination programs in some countries, it has increased in Western countries because of the influx of immigrants, as mentioned above.

Early detecting hepatitis D is important because it has implications for public health. With early treatment, disease progression and complications may be prevented. In one study, delaying HDV screening for more than 5 years was independently associated with worsened liver-related outcomes[8]. In addition, knowledge of HDV coinfection influences treatment decisions because certain newly developed antiviral medications are effective against both HBV and HDV, including bulevirtide[9]. Identifying and managing HDV-positive individuals help reduce the risk of disease transmission, particularly in high-risk settings such as healthcare facilities and households. Screening programs also contribute to public health education by increasing awareness of the risks associated with HBV and HDV coinfection.

Double reflex testing involves anti-HDV testing of all HBsAg-positive individuals, followed by HDV RNA testing for those who test positive for anti-HDV. Owing to the severe implications of coinfection, this test has gained attention, emerging as an effective diagnostic strategy. However, the current practice of diagnosing HDV is stepwise, relying on the physician's discretion and requiring several visits. HDV cases must be identified for timely care management. Reflex testing simplifies the process for both healthcare providers and patients and reduces the bias inherent to physician-led testing.

The universal screening of HBsAg-positive patients helps identify more individuals with HDV infection. If implemented in national hepatitis control programs, it will be more cost-effective in areas with a reported lower prevalence of hepatitis B but a higher prevalence of hepatitis D. The cost-effectiveness depends on the number of HBV-positive patients screened to obtain one patient with hepatitis D. However, considering that the number of newly diagnosed HBV cases has decreased globally, the strategy of reflex testing may be easily implemented by the healthcare systems. Cost-effectiveness studies may be needed in areas with high HDV *vs.* low HDV prevalence.

Several pieces of evidence support double reflex testing. A study conducted at the University of Naples Hospital Federico II in Italy highlighted the impact of implementing reflex testing for HDV in HBsAg-positive individuals. Before reflex testing was introduced, only 16.4% of HBsAg-positive participants were tested for anti-HDV, but after implementation, the percentage increased to 100%. Although the anti-HDV positivity prevalence decreased (from 16.6% to 10.7%), the absolute number of identified anti-HDV-positive patients rose from 14 to 52, with a higher prevalence in immigrant populations, leading to the possibility of more targeted interventions[10]. Therefore, reflex testing substantially improves the detection of HDV infection.

In Spain, one study assessed the impact of HDV reflex testing over 8 years by comparing the previous scenario with the current one (7.6% testing rate) using a proposed universal reflex testing strategy. Results revealed that implementing

reflex testing increased anti-HDV detection; thus, more patients received treatment and achieved undetectable HDV-RNA levels. Liver complications and associated costs were also significantly reduced; thus, reflex testing could decrease the clinical and economic burden of chronic hepatitis D by 35%-38% by 2030[11]. Such modeling could be used to support the drive for double reflex testing with long-term savings, contributing to the increased upfront cost.

Guidelines for HDV screening vary internationally. The European Association for the Study of Liver recommends testing all HBsAg-positive individuals[12]. The American Association for the Study of Liver Diseases focuses on patients at high risk of HDV infection or with active liver disease despite low HBV-DNA levels[13]. However, a United States study showed that a risk-based screening approach would miss 18% of HDV-positive patients because of unreported or negative risk factors[14]. Therefore, reflex anti-HDV testing followed by HDV-RNA testing is now increasingly advocated in the United States. Despite Factors such as awareness, reliable test availability, and cost-effectiveness in different epidemiological settings can influence the adoption of such a program[1]. However, the Chronic Liver Disease Foundation has recently recommended universal HDV screening for all HBsAg-positive patients[15].

CONCLUSION

Double reflex testing is highly recommended in hepatitis D-endemic regions. Modeling should be initially employed to project the cumulative savings attained from this program, which can, in turn, justify the economic impact of increased testing. Furthermore, low-HBV-prevalence and high-HDV-prevalence countries should consider double reflex testing as the preferred strategy[6]. Reflex testing for HDV in HBsAg-positive individuals significantly improves HDV infection detection and management and eases the burden on physicians. Therefore, healthcare providers need to be educated on this program, and government-based hepatitis control programs should implement it.

FOOTNOTES

Author contributions: Abbas Z conceived the theme; A review of the literature was done by Abbas Z and Abbas M; Both authors approved the final version of the manuscript.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: Pakistan

ORCID number: Zaigham Abbas 0000-0002-9513-5324.

S-Editor: Gong ZM

L-Editor: A

P-Editor: Cai YX

REFERENCES

- 1 Negro F, Lok AS. Hepatitis D: A Review. *JAMA* 2023; **330**: 2376-2387 [PMID: 37943548 DOI: 10.1001/jama.2023.23242]
- 2 Miao Z, Zhang S, Ou X, Li S, Ma Z, Wang W, Peppelenbosch MP, Liu J, Pan Q. Estimating the Global Prevalence, Disease Progression, and Clinical Outcome of Hepatitis Delta Virus Infection. *J Infect Dis* 2020; **221**: 1677-1687 [PMID: 31778167 DOI: 10.1093/infdis/jiz633]
- 3 Stockdale AJ, Kreuels B, Henrion MYR, Giorgi E, Kyomuhangi I, de Martel C, Hutin Y, Geretti AM. The global prevalence of hepatitis D virus infection: Systematic review and meta-analysis. *J Hepatol* 2020; **73**: 523-532 [PMID: 32335166 DOI: 10.1016/j.jhep.2020.04.008]
- 4 Chen HY, Shen DT, Ji DZ, Han PC, Zhang WM, Ma JF, Chen WS, Goyal H, Pan S, Xu HG. Prevalence and burden of hepatitis D virus infection in the global population: a systematic review and meta-analysis. *Gut* 2019; **68**: 512-521 [PMID: 30228220 DOI: 10.1136/gutjnl-2018-316601]
- 5 Polaris Observatory Collaborators. Adjusted estimate of the prevalence of hepatitis delta virus in 25 countries and territories. *J Hepatol* 2024; **80**: 232-242 [PMID: 38030035 DOI: 10.1016/j.jhep.2023.10.043]
- 6 Razavi HA, Buti M, Terrault NA, Zeuzem S, Yurdaydin C, Tanaka J, Aghemo A, Akarca US, Al Masri NM, Alalwan AM, Aleman S, Alghamdi AS, Alghamdi S, Al-Hamoudi WK, Aljumah AA, Altraif IH, Asselah T, Ben-Ari Z, Berg T, Biondi MJ, Blach S, Braga WSM, Brandão-Mello CE, Brunetto MR, Cabezas J, Cheinquer H, Chen PJ, Cheon ME, Chuang WL, Coffin CS, Coppola N, Craxi A, Crespo J, De Ledinghen V, Duberg AS, Etzion O, Ferraz MLG, Ferreira PRA, Forns X, Foster GR, Gaeta GB, Gamkrelidze I, García-Samaniego J, Gheorghe LS, Gholam PM, Gish RG, Glenn J, Hercun J, Hsu YC, Hu CC, Huang JF, Janjua N, Jia J, Kåberg M, Kaita KDE, Kamal H, Kao JH, Kondili LA, Lagging M, Lázaro P, Lazarus JV, Lee MH, Lim YS, Marotta PJ, Navas MC, Naveira MCM, Orrego M, Osioy C, Pan CQ, Pessoa MG, Raimondo G, Ramji A, Razavi-Shearer DM, Razavi-Shearer K, Ríos-Hincapié CY, Rodríguez M, Rosenberg WMC, Roulot DM, Ryder SD, Safadi R, Sanai FM, Santantonio TA, Sarrazin C, Shouval D, Tacke F, Tergast TL, Villalobos-Salcedo JM, Voeller AS, Yang HI,

- Yu ML, Zuckerman E; Polaris Observatory. Hepatitis D double reflex testing of all hepatitis B carriers in low-HBV- and high-HBV/HDV-prevalence countries. *J Hepatol* 2023; **79**: 576-580 [PMID: [37030400](#) DOI: [10.1016/j.jhep.2023.02.041](#)]
- 7 **Sagnelli C**, Pisaturo M, Curatolo C, Codella AV, Coppola N, Sagnelli E. Hepatitis B virus/hepatitis D virus epidemiology: Changes over time and possible future influence of the SARS-CoV-2 pandemic. *World J Gastroenterol* 2021; **27**: 7271-7284 [PMID: [34876788](#) DOI: [10.3748/wjg.v27.i42.7271](#)]
- 8 **Kamal H**, Lindahl K, Ingre M, Gahrton C, Karkkonen K, Nowak P, Vesterbacka J, Stål P, Wedemeyer H, Duberg AS, Aleman S. The cascade of care for patients with chronic hepatitis delta in Southern Stockholm, Sweden for the past 30 years. *Liver Int* 2024; **44**: 228-240 [PMID: [37904316](#) DOI: [10.1111/liv.15770](#)]
- 9 **Wedemeyer H**, Aleman S, Brunetto MR, Blank A, Andreone P, Bogomolov P, Chulanov V, Mamonova N, Geyvandova N, Morozov V, Sagalova O, Stepanova T, Berger A, Manuilov D, Suri V, An Q, Da B, Flaherty J, Osinusi A, Liu Y, Merle U, Schulze Zur Wiesch J, Zeuzem S, Ciesek S, Cornberg M, Lampertico P; MYR 301 Study Group. A Phase 3, Randomized Trial of Bulevirtide in Chronic Hepatitis D. *N Engl J Med* 2023; **389**: 22-32 [PMID: [37345876](#) DOI: [10.1056/NEJMoa2213429](#)]
- 10 **Cossiga V**, Brusa S, Montalti R, De Conte A, Jannuzzi G, Ranieri L, Sorrentino R, Vallefuoco L, Pignata L, Guarino M, Portella G, Morisco F. Anti-HDV reflex testing in HBsAg-positive subjects: An efficacious strategy to identify HDV infection. *Liver Int* 2024; **44**: 148-154 [PMID: [37789576](#) DOI: [10.1111/liv.15746](#)]
- 11 **Buti M**, Domínguez-Hernández R, Palom A, Esteban R, Casado MÁ. Impact of hepatitis D reflex testing on the future disease burden: A modelling analysis. *Liver Int* 2023; **43**: 2611-2614 [PMID: [37916574](#) DOI: [10.1111/liv.15776](#)]
- 12 **European Association for the Study of the Liver**. EASL Clinical Practice Guidelines on hepatitis delta virus. *J Hepatol* 2023; **79**: 433-460 [PMID: [37364791](#) DOI: [10.1016/j.jhep.2023.05.001](#)]
- 13 **Terrault NA**, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, Brown RS Jr, Bzowej NH, Wong JB. Update on Prevention, Diagnosis, and Treatment of Chronic Hepatitis B: AASLD 2018 Hepatitis B Guidance. *Clin Liver Dis (Hoboken)* 2018; **12**: 33-34 [PMID: [30988907](#) DOI: [10.1002/cld.728](#)]
- 14 **Nathani R**, Leibowitz R, Giri D, Villarroel C, Salman S, Sehmbhi M, Yoon BH, Dinani A, Weisberg I. The Delta Delta: Gaps in screening and patient assessment for hepatitis D virus infection. *J Viral Hepat* 2023; **30**: 195-200 [PMID: [36458863](#) DOI: [10.1111/jvh.13779](#)]
- 15 **Pan C**, Gish R, Jacobson IM, Hu KQ, Wedemeyer H, Martin P. Diagnosis and Management of Hepatitis Delta Virus Infection. *Dig Dis Sci* 2023; **68**: 3237-3248 [PMID: [37338616](#) DOI: [10.1007/s10620-023-07960-y](#)]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: office@baishideng.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

