National Task Force on Hepatitis B

www.hepbtaskforce.org

Meeting Notes

Date: Wednesday, February 1, 2023 (every 1st Wednesday of the month)
Time: 3PM ET / 2PM CT / 1PM MT / 12PM PT / 10 AM Hawaii
Email: administrator@hepbtaskforce.org

Zoom Meeting registration link: https://us02web.zoom.us/j/81055483671?pwd=YjdPN2RybE03eGpwdVJCZWpSWFJ5Zz09

Attendance (at or after 3:05PM) are as follows:

Executive Board Members (Officers):

☒ **Co-Chair: Carol Brosgart, MD** (San Francisco, CA)
☒ **Co-Chair: Richard So, MPH,** Executive Director, SF Hep B Free – Bay Area (San Francisco, CA)
☒ **Secretary: Yasmin Ibrahim, MD, PhD, MBA,** Senior Program Manager, Hepatitis B Foundation (Doylestown, PA)
☒ **Administrator** (and notetaker)**: Amy Trang, PhD, MEd,** Founder and CEO, Social Capital Solutions (Northern VA)

Regional Directors:

☐ **Northeast Regional Director: Dr. Ponni Perumalswami, MD,** Associate Professor, University of Michigan and Director of the Liver Clinic VA Ann Arbor Healthcare System (Ann Arbor, MI)
☐ **Southeast Regional Director: Vacant**
☐ **North Central Regional Director: Vacant**
☐ **South Central Regional Director: Tzu-Hao "Howard" Lee, MD,** Assistant Professor, Baylor College of Medicine (Houston, TX)
☒ **Western Regional Director: Thaddeus Pham,** Viral Hepatitis Prevention Coordinator, Hawaii State Department of Health (Honolulu, HI)

Student Representation

☐ **APAMSA students**

Board Advisors:

☒ Richard Andrews, MD, MPH, Board Advisor (Houston, TX)
☐ Moon Chen, PHD, MPH, Board Advisor; one of the original founders of the Task Force in 1997 (UC Davis; Sacramento, CA)
☐ Chari Cohen, DrPH, MPH, Board Advisor (Hep B Foundation; Doylestown, PA)
☐ Robert Gish, MD, Board Advisor (Robert G. Gish Consultants; San Diego, CA)
☒ Lu-yu Hwang, MD, Board Advisory (Department of Epidemiology, University of Texas HSC; Houston, TX)
☐ Karen Jiobu, Board Advisor (Asian American Community Services; Columbus, OH)
☐ Amy Tang, MD, Board Advisor (North East Medical Services; San Francisco, CA)

General Members (open to all on listserv; please excuse any typos)**: Total Number of attendees: 17**

- ✓ Saira Khaderi, MD, Baylor St. Luke's Medical Center (Houston, TX)
- ✓ Lizette Gutierrez, Baylor St. Luke's Medical Center (Houston, TX)
- ✓ Julia Freimund, University of Washington School of Medicine (Seattle, WA)
- ✓ Andrew Piotrowski, MA, MAHA (Chicago, IL)
- ✓ Binh Tran, PharmD, APHF and Hep B Free LA (Los Angeles, CA)
- ✓ Julie Yoshimachi, MD, Charles B Wang Community Health Center (New York, NY)
- ✓ Justin Chen, Charles B Wang Community Health Center (New York, NY)
- ✓ Stephanie Campbell, Medical Affairs, Dynavax
- ✓ Thuy Nguyen, MD, Scientist, US National Cancer Institute (Bethesda, MD)
- ✓ Chris Bositis, MD, National Clinician Consultation Center, UCSF (San Francisco, CA)

Note: There may be some members missing from this list of attendees; please excuse any omission.

Agenda:

1) Welcome Task Force members
2) Note any changes to previous meeting's notes
3) Project updates:
    a. HBV universal vaccination guidance promotion among providers (no new updates)
    b. HBV ECHO program
    c. HBV workforce development projects (no new updates)
    d. HBV elimination plan best practices among state Viral Hepatitis Coordinators (no new updates)
    e. HBV work group on updating screening guidance (no new updates)
    f. Upcoming trainings or resources
4) Action Plan discussion: Next steps?
5) Regional Updates (all Regional Directors)
    a. Nominations for Officers and Regional Directors
6) Other items (all members)

Meeting format:

- strategic discussions and resource sharing to assist members with their local work

Notes:

1) Welcome: Introduction / Roll Call of Officers and Regional Directors (Amy Trang)
    a) Opening remarks made by Richard So
    b) Recognize any new members on the call: see list of attendees above
2) Note any changes to previous meeting's notes:
    a) date on the footer should have been January 11, 2023, not January 9, 2023.
3) Project Updates
    a) HBV universal vaccination guidance promotion among providers (no new updates)
    b) HBV ECHO program (Dr. Saira Khaderi and Lizette Gutierrez)
        i) The Texas Echo program combined HBV and HCV programs last month and continues to do well with 2 clinics a month; each session has about 15 attendees. They had 11 cases in the first week. There's still more HCV cases than HBV. Also, Beatrice reached out from Hepatitis B Foundation to share Hep Delta resources and that will be incorporated in the program as well. The hepatitis ECHO program at Baylor is actually hitting a 10 year milestone… with an estimated 2,500 - 3,000 cases (of mostly uninsured individuals) that were reviewed during the past 10 years! Congratulations all around!
        ii) The ECHO program in Philadelphia is still doing well. It's once a month with 30-40 participants, including individuals from other countries (i.e., India, Tanzania, and Nigeria) that join and share their cases.
        iii) The ECHO program in Hawaii finished its 16-week session (4 months program) at the end of last year and is currently taking a break to plan for the next cohort. They are looking to adopt the rotating cohort model for each year. They also had about 30 – 40 consistent attendees each session, including individuals with lived experience as part of the presenting faculty. Storytelling has been a successful part of their program; this included integrating the "Just B" storytelling videos in the sessions.

iv) The University of Washington in Seattle's ECHO program is also going well; they also have a combined hepatitis B and C program.

c) HBV workforce development project (no new updates)

d) HBV elimination plan best practices among state Viral Hepatitis Coordinators (no new updates)

e) HBV work group on updating screening guidance

i) Catherine Freeland shared updates on screening guidelines by CDC; it should be finalized and published in March 2023.

f) Upcoming trainings or resources

i) As the President of the Regional Houston Viral Hepatitis Task Force, Dr. Andrews discussed the AIDS Education and Training Center (AETC) resources and asked if any other states are able to leverage their resources for HBV programs because the money received specifically mentions viral hepatitis, which includes hepatitis B.

(1) Julia Friemund commented that she recently spoke at the Mountain West AETC, which had good resources as well. The hepatologist from the University of Washington was there and talked about hepatitis B diagnosis and management in 2023 and then hepatitis C diagnosis and management. Julie introduced them to hepatitis B online and hepatitis C online. The University of Washington also has the national HIV curriculum online too. All these online training resources are from the University of Washington. In the HIV curriculum, there are 2 lessons on hepatitis B. Links that Julie shared in the chat box:

(a) https://aidsetc.org/directory

(b) https://aidsetc.org/content/hivhcv-co-infection-resources

(c) https://aidsetc.org/resource/hepatitis-b-primary-care

(2) Thaddeus asked Dr. Andrews if he could put together some guidance on how other states could tap into their local resources because it's been a while since he engaged AETC in Hawaii and this would be a great conversation starter to re-engage them.

(3) Amy Trang commented that she'll look into it for DC, MD, and VA. Although, in MD, the HIV grant project has allowed HBI the opportunity to also do hepatitis B work because it reaches the same target population. This may be a good funding source to leverage for those who have not yet considered it for their program expansion in their local areas.

(4) Andrew Piotrowski from Chicago commented that he'll also recheck in his area because there was a conversation about it, but nothing has started yet.

(5) This would be a good opportunity to engage state health departments as well.

(6) Catherine suggested contacting your state hepatitis coalition as a starting point. NVHR has posted the elimination mapping resources as a start for how to be a part of your state's initiatives: https://www.hhs.gov/hepatitis/mapping-hepatitis-elimination-in-action/index.html.

ii) Julia Freimund updated everyone on the 2nd edition of Hepatitis B Online that launched in December; there are new CME/CE opportunities, including advance pharmacology CE for advanced practices. Two new lessons were recently added last month. There should be a total of 10 new lessons now.

(1) As a reminder, those who have already earned CME/CE from the previous edition to earn new CME/CE credits can do the new lessons and get new credits because of the new materials that are available. Program is 100% funded by CDC for continuing medical education so it's free. Here's the link: Hepatitis B Online (uw.edu). It's also posted on the Task Force's website.

(2) Every 3 years, there's a formal review process and application for CME credits.

iii) Stephanie Campbell shared that Dynavax will be doing national webinars around hepatitis B education again soon, but there aren't any specific dates yet.

4) Action Plan discussion: Next steps?

   a) There are lots of great projects going on around the country, we'll continue to share them with Task Force members as we see relevant.

   b) We'll also continue to connect Task Force members offline to relevant resources and use the monthly meetings to share new findings and resources.

   c) Richard So encouraged everyone to look into Quest Diagnostics for funding to do hepatitis B testing. Catherine Freeland added that they have historically provided smaller grants around $10,000 so it's worth looking into for your local area. It would help pay for the cost of phlebotomists and lab work. They need at least 3 weeks of notice.

5) Positions still available for nominations:
   a) Regional Directors:
      i) North Central Region (formerly the North Midwest Region; it's "Central" now based on time zone): still available for nominations.
      ii) Mid-Atlantic Region + Southeast Region (combined position): still available for nominations.

   b) Please continue to nominate and self-nominate to fill these positions.
      i) Submit a short bio and headshot photo to share
      ii) Email: administrator@hepbtaskforce.org
      iii) More information about the roles and responsibilities of these volunteer positions can be found: https://hepbtaskforce.org/our-coalition/governing-structure

   c) It's a great opportunity for anyone looking for larger networking and support for their local programs / project initiatives on hepatitis B; the Task Force helps you connect to resources

6) Regional Updates
   a) Student Representative: (email from Jane Park)
   APAMSA is still in the process of recruiting regional/other students to attend the meeting; once they do, there will be more medical student representatives at each meeting.

   b) Western Region (Thaddeus Pham):
      i) Thaddeus Pham shared updates on the Hepatitis B mortality report that shows the burden on communities in Hawaii. It was recently published in the local journal: https://www.hepfreehawaii.org/news/hep-b-mortality-in-hi-data.

      Thaddeus also shared the idea of creating a "gold card," which was mentioned to providers who attended their ECHO; it was looking into waiving prior authorizations for clients. They're currently working out the details for a proposal. It would be good to have it in case there are future challenges.

      Amy also provided an update on seeking other funders for the in-person summit in Hawaii in November. She'll be submitting a proposal to AbbVie and GSK to get their feedback.

      ii) Richard So provided an update on SF Hep B Free Bay Area's initiative to continue to promote AB 789 (law that passed in California to require health facilities to offer voluntary hepatitis B and C testing).
         (1) The California Department of Public Health has sent out the notice to all clinics and providers, but not much has been done to implement it. Also, there's no way to really enforce it because there aren't any resources to conduct audits, so it's up to the community advocates to really push it to start.
         (2) Stanford University did an evaluation to see if there has been any increase in screening numbers and is looking to publish a paper within the next 2 or 3 months to share findings.

(3) Dr. Carol Brosgart suggested reaching out to Dr. Terry Wright, MD, a hepatologist at GSK in the Bay Area in South San Francisco who may be a good partner for this.

Richard also discussed a very large project in Northern San Mateo County with a funded budget of about $150K from Peninsula Health Care; there's multi-components to the project, with a digital advertising campaign component. They will be engaging nursing students to also do ground work canvassing businesses and educating people on hepatitis B in the city of Milbray. They will also be engaging pharmaceutical companies to help promote the vaccine and local retail pharmacies. Something similar to this was done in San Francisco about 10 years ago. Also, they will have a physician outreach component, which is probably going to be most challenging; CME programs will be offered when appropriate. They also intend to have health fairs to engage physicians, pharmacies, and business sponsors.

(1) Amy Trang inquired about performance measures for the effectiveness of the digital media campaign and potentially sharing the findings and best practices at the Hep B United Summit in July. Other Task Members on the call agreed that that would be a topic of interest and serve as a model for other Task Force members and organizations to learn.
(2) Dr. Carol Brosgart suggested (if not already done) to map out the biotech and high-tech companies in San Mateo area and reach out to their employee health relations department or HR to see if they are interested in partnering and sharing the message with their employees. For example, Genetech.
(3) Thaddeus shared information on https://www.mesmerize.com/. They do in-clinic placement of products and visuals. It's a bit low tech and might be a good resource for Richard So's team to connect to learn more about their resources and "Patient Education at Point of Care."

iii) Dr. Binh Tran shared that APHF in San Diego is having an outreach event Sunday, February 5th; Dr. Gish will be there. They will be officially inducted in the Liver Center at UC San Diego Health, which will make future collaborations with other organizations easier.
iv) Dr. Chris Bositis is still looking for funding opportunities to support the "Hepatitis B Warm Line." Currently, they are taking occasional calls for Hepatis B when they come in, but there's no dedicated call line for it yet. Funding opportunities are still restricted to non-pharmaceutical. They are specifically looking for foundation or government grant opportunities. Dr. Bositis' site (the National Clinician Consultation Center) is also currently a national AETC, so that resource has already been explored. They can't fund themselves because they are one of 2 national AETC sites.

c) North Central Region (vacant):
i) Andrew Piotrowski shared that Maggie's Program Coordinator position at MAHA in Chicago is going to be filled soon; they have interviewed potential candidates and hope to welcome a new member by the next Task Force meeting.

d) South Central Region (Dr. Howard Lee):
i) Dr. Lu-yu Hwang shared the initiatives that Dr. Howard Lee has been taking to reach the Fujian community in Houston to provide more education and screening. Kendra from VBI has also discussed their 3-dose vaccines for this community.
ii) Dr. Howard Lee, Dr. Saira Khaderi, Dr. Lu-yu Hwang, Dr. Jacki Chen, and Dr. Robert Gish are all planning to attend APASL in Taipei, Taiwan (February 15 – 19, 2023).
iii) Dr. Hwang will coordinate with Dr. Richard Andrews to reach out to HOPE Clinic to see how to reach out to the Vietnamese community in Houston, which is the 2nd largest Vietnamese community in the country.

e) Northeast Region (Dr. Ponni Perumalswami):
i) Catherine Freeland shared updates on the Patient storytelling project: https://www.hepb.org/research-and-programs/patient-story-telling-project/. Hepatitis B Foundation is also currently collecting stories from hep B patients outside of the US, including Taiwan and the Philippines. Catherine had collected stories from Nigeria and Tanzania last fall. They are continuing to build their portfolio and diversity of languages. They anticipate having a new website up for that to make it easier to connect to Hep B Storytellers.

(1) Amy Trang commented that they could potentially collect stories from Vietnam in June, if interested.
(2) Also, there's a Hep B Consult Line at the hepatitis B foundation: (215)489-4900
(3) Thaddeus also acknowledged Hep B Foundations' translations of the Patient Hep B Guide as a great resource for his work: https://urldefense.com/v3/__https://www.hepb.org/resources-and-support/fact-sheets/__;!!LIYSdFfckKA!zytyvt74eCTUSmNWyyfbbRI6VDyy9iYo8FmPabh3eiV0qLzS0RcuZoj6EcoI5ghdM-0sZL2JunrROz8P2EjKLaPbUFFp5fkLtm0s$
(4) Hepatitis B Foundation is reaching out to Task Force members for connections to storytellers; this will entail a training at the end of July or August this year. Storytellers will be compensated.

In Philadelphia, they are planning a Hepatitis B Elimination Summit for May 19th and record it. They expect to have representatives from CDC there as well as city and state officials to talk about elimination planning and getting involved, connected, and plugged-in as champions in the city. They will be working with Prevention Point Philadelphia, which is a harm reduction facility.

Also, they are going to be doing hepatitis B assessments to figure out barriers and facilitators to hepatitis B and delta testing as well as qualitative work. This includes interviewing providers and doing a survey to gather networks' feedback. This will also lead to doing screenings as part of the program and hopefully vaccinations if they're able to get donations.

ii) Dr. Julie Yoshimachi is the new Hepatitis B Care Program Director at Charles B. Wang Community Health Center. CBWCHC is working on increasing hepatitis B outreach in New York City. Additional information was shared by Justin Chen, CBWCHC Research and Evaluation Program Associate via email.
Two upcoming workshops:
(1) 2/9/2023 at NY Golden Eagle Senior Center
(2) 2/21/2023 at Asian Americans for Equality

The first workshop is for Chinese seniors. The second workshop is for new Chinese immigrants. Even though these workshops are limited to specific populations at the moment, we do hope to expand our educational workshops to other populations in NYC and increase hep B screenings.

f) Southeast Region (vacant):
i) HBI has a new Deputy Executive Director, Sandra Ashford. Jane Pan is transitioning into retirement.
ii) Dr. Thuy Nguyen from NIH National Cancer Institutes shared that she's currently working on a hepatitis B study in Vietnam with around 700 patients. They recently got a grant from Gilead. It will be the first time that there's a collaboration between a public institution in Vietnam and the National Cancer Institute in the US for this kind of study. If anyone on the Task Force has any ideas for other future studies, please feel free to share and brainstorm.

7) Other items: (not discussed in the meeting)

Meeting adjourned at 4:00PM Eastern Time.

- Next Hep B Task Force Zoom meeting date: **Wednesday, March 1, 2023 at 3PM Eastern Time** /2PM Central/ 1PM Mountain/ 12PM Pacific / 10 AM Hawaii (1st Wednesday of each month).
  - Other dates in 2023: April 5, May 3, September 6, October 4, and December 6
  - No meetings in June, July, August, and November; activities will continue to be shared via email

- Suggestions for the next agenda:
  - Highlights from the APASL conference in Taiwan (Dr. Howard Lee, Dr. Saira Khaderi, Dr. Lu-yu Hwang, Dr. Jacki Chen, Dr. Robert Gish, and anyone else who attended)
  - Projects and resource updates and discussions:
    - Focus on members' projects, provider education resources, and funding opportunities to share
  - Review nominations for 2 vacant Regional Director positions for the next 2-years (if any)

- The National Task Force on Hepatitis B is a volunteer-based national coalition and is independent from the state and local Task Forces or coalitions. Everyone is welcome to join the National Task Force on Hepatitis B by registering through our website. Newsletter - The National Task Force on Hepatitis B (hepbtaskforce.org). Promotion of the National Task Force on Hepatitis B is primarily through "word-of-mouth" and personal communication.

Upcoming HBV ECHO sessions: Free CME

Gulf Coast (Texas Heart Institute with Baylor St. Luke Medical Center): Project ECHO Interest Form (bcm.edu)

- Every 2nd and 4th Monday of the month
- 12:00PM to 1:00PM Central Time
- To register: Project ECHO Interest Form (bcm.edu)

East Coast (Hep B United Philadelphia): Hepatitis B ECHO Meeting Registration - Zoom

- Every 4th Thursday of the month
- 12:00PM – 1:00PM Eastern Time
- To register: Meeting Registration - Zoom

Other ECHO programs with HBV:

- The University of Washington Project ECHO Viral Hepatitis meets every Tuesday, 12 – 1:30 PM Pacific Time.
- To discuss if this ECHO program would be a good fit or if other training or consult options would better suit your interests/schedules, please email Pam Landinez, landinez@uw.edu.
- The sessions are geared towards individuals in the state of Washington and focus on hepatitis B or C is driven by the program participants.

Upcoming international HBV conferences:

- The Asian Pacific Association for the Study of the Liver (APASL) 2023
  - Taipei, Taiwan
  - February 15-19, 2023
  - Registration link: APASL 2023
- The 18th International Symposium of Viral Hepatitis and Liver Diseases (ISVHLD) Global Hepatitis Summit 2023
  - Paris, France
  - April 25 – 28, 2023
  - Registration link: Global Hepatitis Summit 2023 |Home (global-hepatitis.com)
- The European Association for the Study of the Liver (EASL) 2023
  - Vienna, Austria
  - June 21 – 24, 2023
  - Registration link: EASL Congress 2023 | 21-24 June 2023 | Vienna, Austria
- American Association for the Study of Liver Diseases (AASLD) Liver Meeting 2023
  - Boston, MA
  - November 10 – 14, 2023
  - No Registration link yet

Items shared via email:

- From Nancy Fenlon, RN, MS (CDC Perinatal hepatitis B Prevention Program): The CDC PHBPP staff is delighted to announce that the Discrepant Prenatal HBsAg Labs resource document has been finalized and is ready to distributed. The document is attached and will be posted on the PHBPP webpage at Perinatal Hepatitis B Prevention Program | CDC in the Resources Section soon. I would like to give a big shout out to Dr. Lakshmi Panagiotakopoulos (and all the Division of Viral Hepatitis staff who contributed) for all her dedication and hard work on this document from concept to realization. Attachment to follow in these meeting notes.

- Dr. Robert Gish, MD, also shared articles and resources (attached at the end of the meeting notes) that may be of interest to Task Force members, including:
    - Rumgay, H., et. al. (2022). Global burden of primary liver cancer in 2020 and predictions to 2040. *Journal of Hepatology*, 77, 1598-1606.
    - Wong, D.K, et. al. (2023). A longitudinal study to detect hepatitis B surface and core-related antigens in chronic hepatitis B patients with hepatitis B surface antigen seroclearance using highly sensitive assays. *Journal of Clinical Virology*, 160, 105375.
    - Wong, R.J., et. al. (2022). Low Performance of Hepatitis Delta Virus Testing Among 2 National Cohorts of Chronic Hepatitis B Patients in the United States. *The American Journal of Gasteroenterology*, 117, 2067-2070.

Discrepant Hepatitis B surface antigen (HBsAg) lab results during pregnancy: recommended next steps

Purpose: A guide for determining management of infants born to a pregnant person with an initial confirmed HBsAg positive result followed by a negative result during the same pregnancy*

Example: HBsAg positive (1st trimester)→HBsAg negative (3rd trimester)

KEY POINTS:

- All positive HBsAg results in pregnancy should be followed by a Nucleic Acid Test (NAT) for Hepatitis B Virus (HBV) DNA (ACIP)
  - » Detection of HBV DNA indicates current HBV infection during pregnancy†
  - » Additional tests for total anti-HBc, IgM anti-HBc and anti-HBs will help establish diagnosis§
- If a definitive diagnosis of HBV infection is not yet established at the time of delivery, the infant should be given hepatitis B vaccine within 12 hours of birth while additional labs are pending
  - » Infants weighing < 2000g should also receive hepatitis B immune globulin (HBIG) within 12 hours of birth if diagnosis cannot be established
  - » If testing confirms diagnosis of HBV infection, infants weighing ≥ 2000g should be given HBIG within 7 days of birth
  - » If a definitive diagnosis cannot be established (e.g., person refuses additional testing), consider managing conservatively and administering HBIG within 7 days of birth
- Refer all HBsAg positive pregnant persons to the Perinatal Hepatitis B Prevention Program (PHBPP) coordinator for case management of mother and infant.

* For pregnant persons never treated or diagnosed with chronic hepatitis B

† Pregnant person should be referred to Perinatal Hepatitis B Prevention Program (PHBPP) and the infant should receive hepatitis B vaccine and hepatitis B immune globulin within 12 hours of birth.

§ If additional tests are not drawn and HBV infection cannot be ruled out, manage as if it is an HBV infection, i.e., refer to PHBPP, give the infant hepatitis B vaccine and HBIG within 12 hours of birth.

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

CS 336498-A February 02, 2023

Table. Interpretation of HBV markers of infection following discrepant HBsAg lab results during pregnancy

HBsAg results: First HBsAg positive and second HBsAg negative in same pregnancy

Additional Tests*	Results of additional testing†	Interpretation	Action
HBV DNA **Total anti-HBc** **IgM anti-HBc** **Anti-HBs**	Detected Positive Positive Positive	Resolving acute infection§	• Refer to PHBPP • **Infant needs post-exposure prophylaxis¶**
HBV DNA **Total anti-HBc** **IgM anti-HBc** **Anti-HBs**	Not detected Positive Negative Negative	False positive HBsAg** (first test) with a history of HBV infection cleared prior to pregnancy OR False negative HBsAg (second test) possible mutant††	• Refer to PHBPP • **Infant needs post-exposure prophylaxis§§**
HBV DNA **Total anti-HBc** **IgM anti-HBc** **Anti-HBs**	Detected Positive Negative Negative	Occult infection	• Refer to PHBPP • **Infant needs post-exposure prophylaxis**
HBV DNA **Total anti-HBc** **IgM anti-HBc** **Anti-HBs**	Detected Positive Positive Negative	Chronic HBV infection with false negative HBsAg (possible mutant††)	• Refer to PHBPP • **Infant needs post-exposure prophylaxis**
HBV DNA **Total anti-HBc** **IgM anti-HBc** **Anti-HBs**	Not detected Positive Negative Positive	False positive HBsAg**(first test) with a history of HBV infection cleared prior to pregnancy OR resolved acute infection during pregnancy	• Refer to PHBPP • **Infant needs post-exposure prophylaxis§§**
HBV DNA **Total anti-HBc** **IgM anti-HBc** **Anti-HBs**	Not detected Negative Negative Negative	False positive HBsAg**(first test) and potentially susceptible¶¶	• Do not refer to PHBPP • **Vaccinate infant per routine guidelines**
HBV DNA **Total anti-HBc** **IgM anti-HBc** **Anti-HBs**	Not detected Negative Negative Positive	False positive HBsAg**(first test) and potentially vaccinated	• Do not refer to PHBPP • **Vaccinate infant per routine guidelines**

* Additional tests should be done on either the same day or after the second HBsAg negative result

† If additional tests are not drawn and HBV infection cannot be ruled out, manage as if it is an HBV infection, i.e., refer to PHBPP, give the infant hepatitis B vaccine and HBIG within 12 hours of birth.

§ HBV exposure early in pregnancy

¶ Post-exposure prophylaxis: administer HBIG and hepatitis B vaccine to the infant within 12 hours of birth

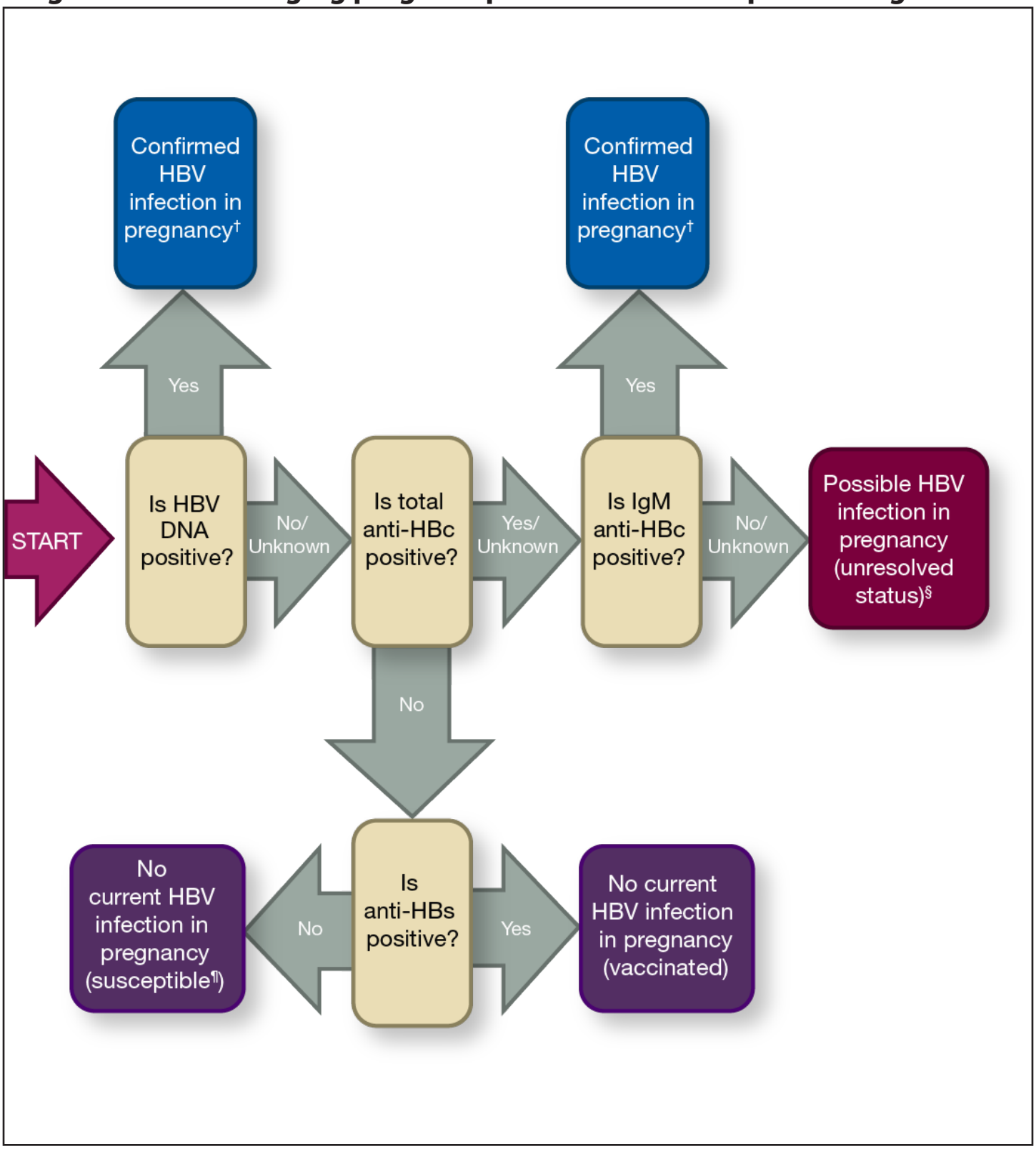
** False positive HBsAg can occur within 30 days of receiving hepatitis B vaccine

†† Mutant HBV that is not detected on second HBsAg test. Some mutant HBV isolates may be undetectable by HBsAg assays that have not yet incorporated these mutants in their assay systems. FDA-approved Abbott ARCHITECT HBsAg assay and Siemens Centaur HBsAg II assays can detect most commonly occurring HBV mutants

§§ Cannot rule out HBV exposure during pregnancy

¶¶ Susceptible persons should be vaccinated according to ACIP recommendations

Algorithm for managing pregnant persons with discrepant HBsAg results*



* For persons never treated or diagnosed with chronic hepatitis B, with an initial confirmed HBsAg positive result followed by a negative result in the same pregnancy.

† Administer Hepatitis B immune globulin (HBIG) and Hepatitis B vaccine to infant within 12 hours of birth and refer to Perinatal Hepatitis B Prevention Program (PHBPP)

§ Infants born to pregnant persons with unresolved HBV infection status should be treated as born to an unknown HBsAg status pregnant person with Hepatitis B vaccine within 12 hours of birth for infants weighing ≥ 2000g and Hepatitis B vaccine and HBIG within 12 hours of birth for infants weighing < 2000g.

° Perform additional testing in pregnant person at the time of delivery. If results are consistent with true infection, refer to PHBPP.

¶ Susceptible persons should be vaccinated according to ACIP recommendations

References:

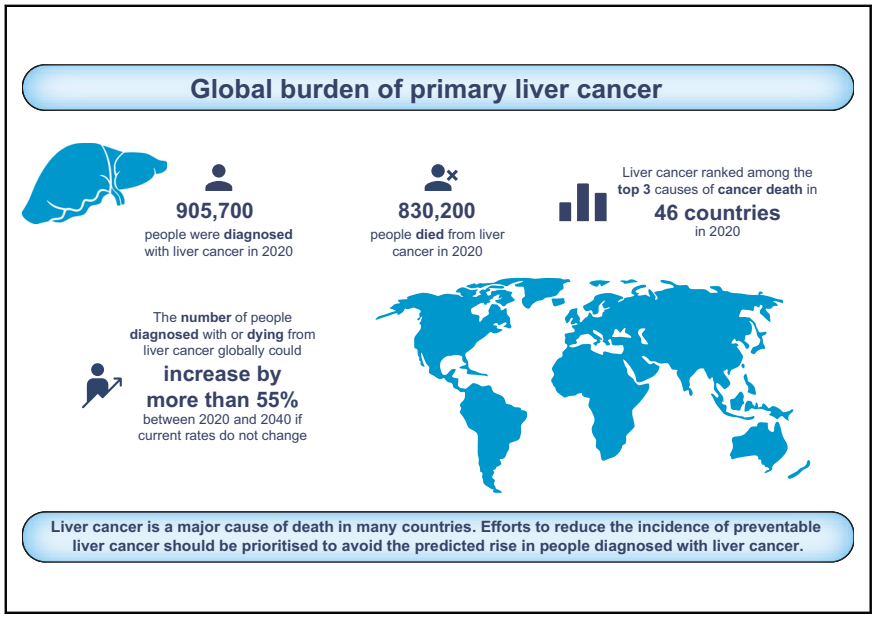
- Interpretation of Hepatitis B Serologic Test Results
- Prevention of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices (cdc.gov)
- Universal Hepatitis B Vaccination in Adults Aged 19–59 Years: Updated Recommendations of the Advisory Committee on Immunization Practices — United States, 2022 | MMWR (cdc.gov)
- Management of Infants Born to Women with Hepatitis B Virus Infection for Pediatricians (cdc.gov)
- Screening and Referral Algorithm for Hepatitis B Virus (HBV) Infection Among Pregnant Women (cdc.gov)
- Hepatitis B Management: Guidance for the Primary Care Provider - HBV Primary Care Workgroup - Hepatitis B Online (uw.edu)
- Update on Prevention, Diagnosis, and Treatment of Chronic Hepatitis B: AASLD 2018 Hepatitis B Guidance
- Discrepant Hepatitis B Surface Antigen Results in Pregnant Women Screened to Identify Hepatitis B Virus Infection

Research Article
Hepatic and Biliary Cancer

JOURNAL
OF HEPATOLOGY

Global burden of primary liver cancer in 2020 and predictions to 2040

Graphical abstract



Highlights

- 905,700 people were diagnosed with and 830,200 people died from liver cancer globally in 2020.
- Liver cancer was among the top three causes of cancer death in 46 countries.
- The number of new cases and deaths from liver cancer could rise by >55% by 2040.

Authors

Harriet Rumgay, Melina Arnold, Jacques Ferlay, …, Mathieu Laversanne, Katherine A. McGlynn, Isabelle Soerjomataram

Correspondence

RumgayH@iarc.who.int (H. Rumgay).

Lay summary

The burden of liver cancer varies across the world. Liver cancer was among the top three causes of cancer death in 46 countries and was among the top five causes of cancer death in 90 countries worldwide. We predict the number of cases and deaths will rise over the next 20 years as the world population grows. Primary liver cancer due to some causes is preventable if control efforts are prioritised and the predicted rise in cases may increase the need for resources to manage care of patients with liver cancer.

https://doi.org/10.1016/j.jhep.2022.08.021

Research Article
Hepatic and Biliary Cancer

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Global burden of primary liver cancer in 2020 and predictions to 2040

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Background & Aims: The burden of liver cancer varies across the world. Herein, we present updated estimates of the current global burden of liver cancer (incidence and mortality) and provide predictions of the number of cases/deaths to 2040.

Methods: We extracted data on primary liver cancer cases and deaths from the GLOBOCAN 2020 database, which includes 185 countries. Age-standardised incidence and mortality rates (ASRs) per 100,000 person-years were calculated. Cases and deaths up to the year 2040 were predicted based on incidence and mortality rates for 2020 and global demographic projections to 2040.

Results: In 2020, an estimated 905,700 people were diagnosed with, and 830,200 people died from, liver cancer globally. Global ASRs for liver cancer were 9.5 and 8.7 for new cases and deaths, respectively, per 100,000 people and were highest in Eastern Asia (17.8 new cases, 16.1 deaths), Northern Africa (15.2 new cases, 14.5 deaths), and South-Eastern Asia (13.7 new cases, 13.2 deaths). Liver cancer was among the top three causes of cancer death in 46 countries and was among the top five causes of cancer death in 90 countries. ASRs of both incidence and mortality were higher among males than females in all world regions (male:female ASR ratio ranged between 1.2–3.6). The number of new cases of liver cancer per year is predicted to increase by 55.0% between 2020 and 2040, with a possible 1.4 million people diagnosed in 2040. A predicted 1.3 million people could die from liver cancer in 2040 (56.4% more than in 2020).

Conclusions: Liver cancer is a major cause of death in many countries, and the number of people diagnosed with liver cancer is predicted to rise. Efforts to reduce the incidence of preventable liver cancer should be prioritised.

Lay summary: The burden of liver cancer varies across the world. Liver cancer was among the top three causes of cancer death in 46 countries and was among the top five causes of cancer death in 90 countries worldwide. We predict the number of cases and deaths will rise over the next 20 years as the world population grows. Primary liver cancer due to some causes is preventable if control efforts are prioritised and the predicted rise in cases may increase the need for resources to manage care of patients with liver cancer.

Introduction

The global burden of liver cancer is substantial. According to 2020 estimates, liver cancer is the sixth most commonly diagnosed cancer and the third most common cause of cancer death.[1] Liver cancer also ranks as the second most common cause of premature death from cancer.[2] Incidence and mortality rates of liver cancer have dropped in some Eastern Asian countries including Japan, China, and the Republic of Korea, but rates have increased in many previously low-incidence countries across the world, such as the US, Australia, and several European countries.[3]

Risk factors for liver cancer include older age and sex (higher risk among males than females), and there are some differences in risk by ethnicity.[4] For example, in multi-ethnic populations such as the US, American Indians/Alaskan Natives, Hispanic persons, non-Hispanic Black persons and Asians/Pacific Islanders have higher rates than non-Hispanic White persons.[4] Although HBV and HCV infections constitute the most important exogenous risk factors for primary liver cancer, excessive alcohol consumption and the related conditions of metabolic syndrome, type 2 diabetes, obesity, and non-alcoholic fatty liver disease have also become prominent causes of primary liver cancer.[4,5] Further exogenous risk factors include cigarette smoking, ingestion of aflatoxin-contaminated food, and liver fluke infestation.[5] Recent studies suggest that approximately 56% of liver cancer is related to HBV and 20% is related to HCV.[6] A further 18% of liver cancer burden may be related to tobacco smoking,[7] and an estimated 17% could be attributable to alcohol drinking globally,[8] with the possibility of multiple risk factors being attributed to the same cases or deaths.

An updated evaluation of the global burden of liver cancer incidence and mortality is warranted due to the disparities in burden across populations and the availability of more recent estimates. In this analysis, we describe where liver cancer ranks amongst all cancer types for cancer diagnoses and deaths in nations across the world. We also present predictions of the future liver cancer burden to 2040.

Keywords: Hepatocellular carcinoma; intrahepatic cholangiocarcinoma; epidemiology; cancer registries.
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Materials and methods

The number of new cases of, and deaths from, primary liver cancer (ICD-10 C22), were obtained from the GLOBOCAN 2020 database for 185 countries and territories, by sex and 18 age groups (0–4, 5–9, …, 80–84, 85 and over).[1,2,9] Corresponding population data for 2020 were extracted from the United Nations (UN) website.[10] The data sources and hierarchy of methods used in compiling the cancer estimates have been described in detail elsewhere.[9] Briefly, the GLOBOCAN estimates are assembled at the national level using the best available sources of cancer incidence and mortality data within a given country.

We predicted the future number of primary liver cancer cases and deaths up to the year 2040 based on the medium-variant UN population projections and the current global-level incidence and mortality rates of primary liver cancer for 2020. The predicted number of new cancer cases or deaths was computed by multiplying the age-specific incidence or mortality rates for the world for 2020 by the corresponding projected world population estimate. These expected populations differ from that of 2020 in terms of age structure and size. The key assumption is that national rates, as estimated in 2020, will not change between 2020 and 2040 and thus changes in number of cases or deaths are solely due to the growth and aging of the population. To show the impact of changes in rates on the future primary liver cancer burden, we also predicted number of cases and deaths from seven scenarios of uniformly increasing or decreasing rates by 3%, 2%, and 1% annually from the baseline year of 2020 to 2040.

We present estimates of new cases and deaths and age-standardised incidence and mortality rates (ASRs) per 100,000 person-years based on the 1966 Segi-Doll World standard population.[11,12] Male:female ratios (M:F) of incidence and mortality ASRs are presented. Cases, deaths, and ASRs of primary liver cancer are presented by country, by 19 world regions based on UN definitions,[10] and by the UN's four-tier Human Development Index (HDI) in 2020,[13] the latter being a means to assess the burden, the strength of health systems, and the ability to report primary liver cancer cases and deaths at varying levels of development (low, medium, high and very high HDI). Rankings were based on number of new cancer cases and deaths by cancer type according to ICD-10 three-digit groupings and not including non-melanoma skin cancer (ICD-10 C44). For comparison of current liver cancer burden with the population prevalence of risk factors for liver cancer, the population attributable fractions of liver cancer due to HBV or HCV infection, alcohol consumption, and high body mass index were obtained from three global studies,[6–8] and are presented in Fig. S1.

Results

Global burden of liver cancer incidence and mortality

An estimated 905,700 people were diagnosed with, and 830,200 people died from, liver cancer globally in 2020 (Table 1). This equated to total ASRs for liver cancer of 9.5 and 8.7 new cases and deaths, respectively, per 100,000 people. More than half of the world's estimated cases and deaths from liver cancer

Table 1. Estimated number of primary liver cancer cases and deaths, and age-standardised incidence and mortality rates per 100,000 persons in 2020, by world region and HDI.

	Population		Incidence				Mortality			
	Total (thousands)	Percentage of world total (%)	Number of cases	Percentage of world total (%)	ASR	M:F	Number of deaths	Percentage of world total (%)	ASR	M:F
Eastern Africa	445,406	5.7	12,300	1.4	5.0	1.6	11,500	1.4	4.8	1.6
Middle Africa	179,595	2.3	6,100	0.7	6.1	2.3	5,700	0.7	5.9	2.3
Northern Africa	246,233	3.2	31,900	3.5	15.2	1.9	30,400	3.7	14.5	1.9
Southern Africa	67,504	0.9	2,600	0.3	4.6	2.2	2,400	0.3	4.3	2.3
Western Africa	401,861	5.2	17,600	1.9	8.4	2.0	16,900	2.0	8.2	2.0
Caribbean	43,532	0.6	3,400	0.4	5.5	1.6	3,200	0.4	5.0	1.6
Central America	179,670	2.3	11,800	1.3	6.3	1.2	11,200	1.4	5.9	1.2
South America	430,760	5.5	24,300	2.7	4.3	1.6	23,200	2.8	4.1	1.6
Northern America	368,870	4.7	46,600	5.1	6.8	2.7	34,800	4.2	4.7	2.4
Eastern Asia	1,678,090	21.5	491,700	54.3	17.8	3.0	449,500	54.1	16.1	3.1
China	1,447,470	18.6	410,000	45.3	18.2	3.1	391,200	47.1	17.2	3.0
South-Eastern Asia	668,620	8.6	99,300	11.0	13.7	3.0	95,700	11.5	13.2	3.0
South-Central Asia	2,014,709	25.8	54,700	6.0	3.0	2.0	52,800	6.4	2.8	2.0
India	1,380,004	17.7	34,700	3.8	2.6	2.3	33,800	4.1	2.5	2.3
Western Asia	278,429	3.6	11,300	1.3	4.7	1.9	10,900	1.3	4.5	1.9
Central-Eastern Europe	293,013	3.8	24,800	2.7	4.3	2.6	23,000	2.8	3.9	2.6
Northern Europe	106,261	1.4	11,900	1.3	5.0	2.1	10,500	1.3	3.9	2.1
Southern Europe	153,423	2.0	24,800	2.7	6.7	3.3	21,200	2.6	5.1	3.2
Western Europe	196,146	2.5	26,100	2.9	5.4	3.3	23,700	2.8	4.5	3.1
Australia/New Zealand	30,322	0.4	3,300	0.4	6.1	3.3	2,500	0.3	4.1	2.7
Melanesia, Micronesia & Polynesia	12,356	0.2	1,100	0.1	11.3	1.7	1,000	0.1	11.2	1.7
Low HDI	990,175	12.7	33,100	3.7	6.2	1.8	31,600	3.8	6.0	1.8
Medium HDI	2,327,556	29.9	100,000	11.0	4.7	2.3	95,900	11.5	4.5	2.3
High HDI	2,909,468	37.3	548,900	60.6	14.0	2.8	524,300	63.2	13.3	2.8
Very high HDI	1,564,286	20.1	223,300	24.7	7.0	2.8	178,100	21.5	5.1	2.8
World	7,794,799	100.0	905,700	100.0	9.5	2.7	830,200	100.0	8.7	2.7

ASR, age-standardised rate per 100,000; HDI, Human Development Index; M:F, male:female ASR ratio.

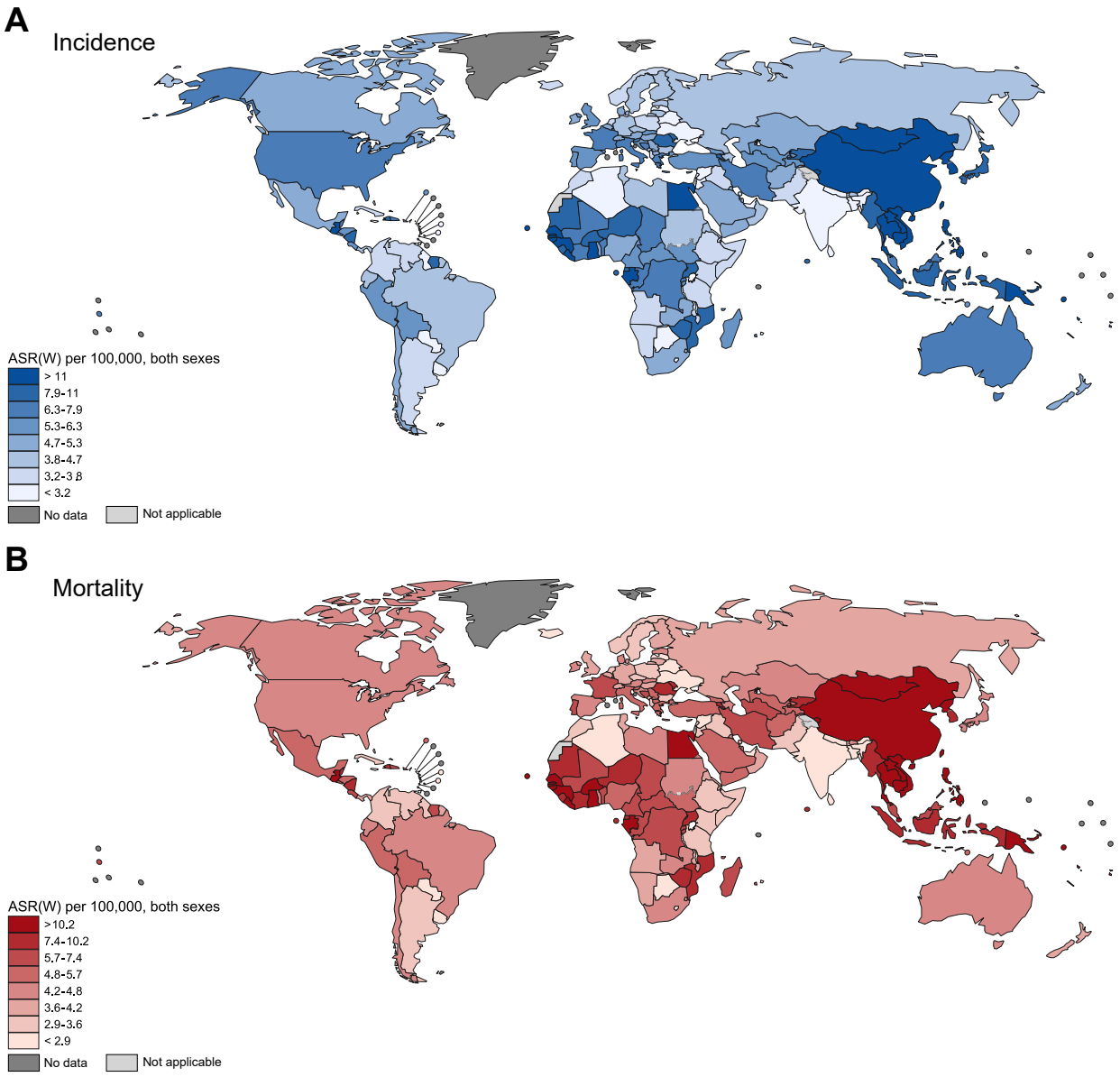

Fig. 1. ASRs for primary liver cancer per 100,000 people in 2020, by country. (A) Age-standardised incidence rate. (B) Age-standardised mortality rate. ASR(W), age-standardised rate. (This figure appears in color on the web.)

occurred in Eastern Asia (54.3% and 54.1%, respectively), which was home to 21.5% of the world's population in 2020. China alone was home to 45.3% of the world's liver cancer cases and 47.1% of liver cancer deaths.

The ASRs of liver cancer incidence ranged 6-fold between world regions, from 3.0 new cases per 100,000 people in South-Central Asia to 17.8 in Eastern Asia. The pattern of mortality ASRs was similar. Eastern Asia had an ASR of 16.1 per 100,000 people compared with 2.8 in South-Central Asia, also resulting in a 6-fold difference. Elevated ASRs for incidence and mortality were also found in Northern Africa (15.2 new cases, 14.5 deaths) and South-Eastern Asia (13.7 new cases, 13.2 deaths). Disparities by sex were apparent, with liver cancer incidence and mortality ASRs higher among males than females in all regions. The incidence M:F ratio ranged from 1.2 in Central America to 3.3 in Southern and Western Europe, and Australia/New Zealand; the mortality M:F ratio was also lowest in Central America (1.2), and was highest in Southern Europe (3.2), Western Europe, and Eastern Asia (both 3.1).

At the national level, ASRs of liver cancer incidence were highest in Mongolia (85.6 new cases per 100,000 people), Egypt (34.1), Laos (24.4), and Cambodia (24.3), and lowest in Sri Lanka (1.2), Saint Lucia (1.3), Algeria (1.5), and Botswana (1.5) (Fig. 1). Mortality ASRs showed a similar pattern as incidence. The full results for number of cases and deaths, and ASRs of liver cancer by country are available in Table S1.

By HDI group, the largest burdens of liver cancer cases and deaths were in high HDI countries, representing 60.6% of new cases and 63.2% of deaths globally. The high HDI group also had the highest rates of incidence (14.0 new cases per 100,000

people) and mortality (13.3 deaths per 100,000 people). This large contribution to the world's liver cancer burden was not unexpected as the high HDI group includes some of the countries with the highest rates of liver cancer incidence and mortality, such as Mongolia, Egypt and China. ASRs were similar across the remaining groups, ranging between 4.5 and 7.0. A correlation between a country's HDI and ASRs for liver cancer incidence or mortality was not observed (Fig. S2).

Ranking of liver cancer diagnoses and deaths

Globally, liver cancer ranked as the sixth most commonly diagnosed cancer and the third most common cause of cancer death in 2020. At the national level, liver cancer was the most commonly diagnosed cancer in six countries (Cambodia, Egypt, Laos, Mongolia, Thailand, and Vietnam) and was among the top three most commonly diagnosed cancers in a total of 18 countries (Fig. 2). In terms of mortality, liver cancer was the most common cause of cancer death in 15 countries (Burkina Faso, Cambodia, Egypt, Gabon, The Gambia, Ghana, Guatemala, Laos, Mongolia, Nicaragua, Republic of Congo, Solomon Islands, Thailand, Vanuatu, and Vietnam) and was among the top three causes of cancer death in a total of 46 countries worldwide. Liver cancer was among the top five causes of cancer death in 90 countries. Most of these countries were in Eastern and South-Eastern Asia, Northern and Western Africa, and Central America. However, liver cancer was also one of the top five causes of

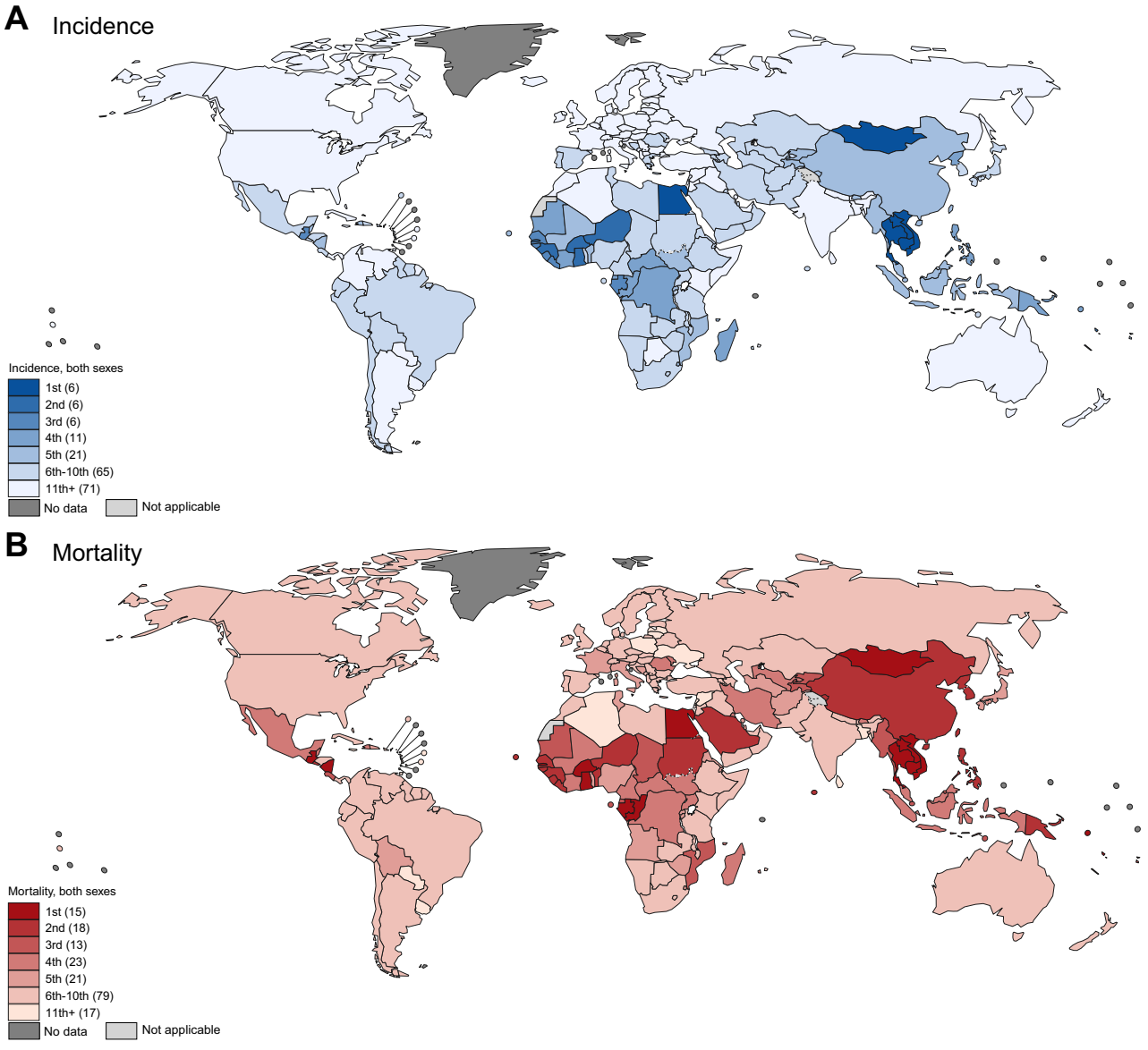

Fig. 2. Ranking of primary liver cancer among other cancer types based on number of cases or deaths in 2020, by country. (A) Number of cases. (B) Number of deaths. (This figure appears in color on the web.)

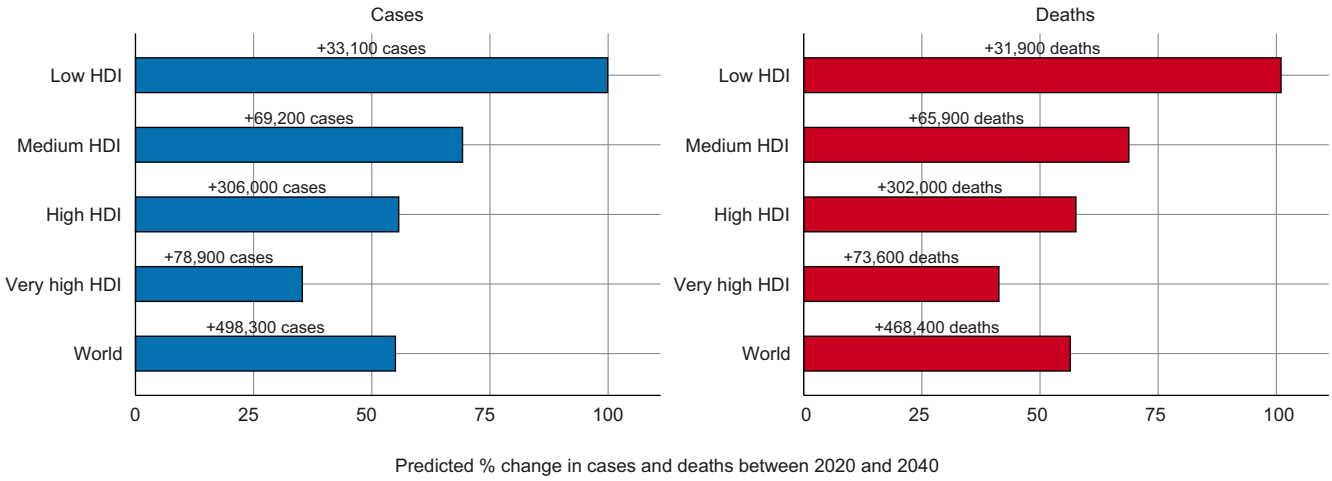

Fig. 3. Predicted percentage change (absolute numbers are shown above bars) of new cases and deaths from primary liver cancer between 2020 and 2040, by HDI. HDI, Human Development Index. (This figure appears in color on the web.)

cancer mortality in some countries in Europe (Bosnia and Herzegovina, France, Italy, Republic of Moldova, and Romania) and Western Asia (Iran, Saudi Arabia, Turkmenistan, and Uzbekistan).

Predicted number and percentage increase of cases and deaths from liver cancer

The number of new cases of liver cancer is predicted to increase by 55.0% between 2020 and 2040, with 1.4 million new diagnoses forecast for 2040 (Fig. 3). An estimated 1.3 million deaths are predicted to occur in 2040, an increase of 56.4%. By HDI group, the highest absolute increase in cases and deaths could occur in high HDI countries, with 55.7% more cases (306,000 additional cases) and 57.6% more deaths (302,000 additional deaths) per year by 2040, reflecting the already elevated rates in the high HDI group and its large population which is predicted to continue to grow. However, the largest relative increases in cases and deaths are predicted to occur in low HDI countries (99.9% and 101.0% increases, respectively) and medium HDI countries (69.2% and 68.8% increases, respectively), due to the predicted growth and aging of the population.

Predictions including annual changes in rates from seven scenarios (−3% to +3% annual change in ASRs) showed a potential increase in the annual number of liver cancer cases and deaths by 2040 in all scenarios except the scenario in which a 3% decrease in ASRs per year is achieved (Fig. 4).

Discussion

Globally, in 2020, an estimated 900,000 people were diagnosed with, and 830,000 people died from liver cancer. Liver cancer

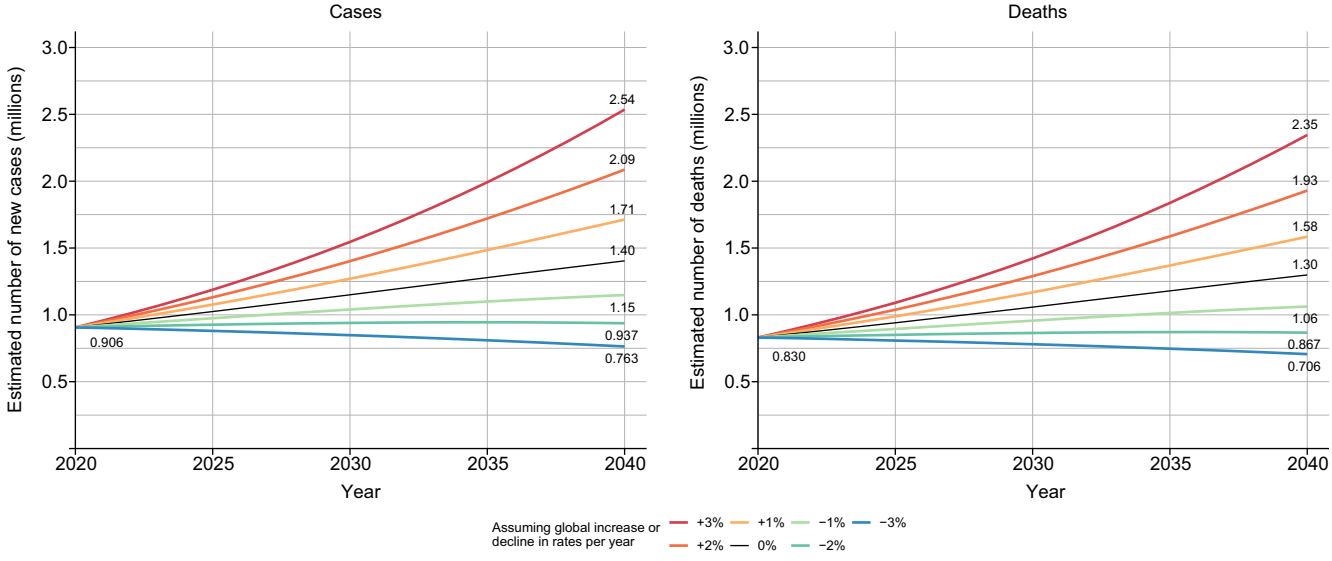

Fig. 4. Predicted number of new cases and deaths from primary liver cancer assuming seven scenarios of annual change in global rates between 2020 and 2040. (This figure appears in color on the web.)

incidence and mortality rates were highest in Eastern Asia, Northern Africa, and South-Eastern Asia, and liver cancer was the most common cause of cancer death in 15 countries including several countries in South-Eastern Asia and sub-Saharan Africa. The number of new cases and deaths from liver cancer are predicted to rise by more than 50% over the next 20 years, assuming current rates do not change, with the burden set to increase unless a 3% or greater annual decrease in rates is achieved.

Liver cancer was among the top three causes of cancer death in 46 countries, and among the top five in 90 countries in 2020, despite not being the most commonly diagnosed cancer in the majority of countries across the world. Moreover, liver cancer was the second most common cause of premature death from cancer in 2020, after lung cancer, with more than 530,000 deaths among persons aged 30 to 69 years.[2] Survival from liver cancer remains poor even in high-income countries. A recent study of seven high-income countries reported that the highest 3-year net survival from liver cancer occurred in Australia (28%) and the lowest occurred in Denmark (17%) in 2012–2014.[14] The results of another study found that 5-year survival during 2010–2014 ranged from less than 10% in several European countries to 30% in Japan, and changed very little over a 20 year time-period.[15] With few improvements in survival in recent decades, primary prevention of liver cancer is key in reducing its burden globally.

Liver cancer due to some major risk factors with large attributable fractions is potentially preventable. For example, chronic HBV infection, which is responsible for more than half of liver cancer cases globally,[6] is most prevalent in sub-Saharan African countries, some South-East Asian countries, and Central Asia[16] which is where the highest proportions of liver cancer attributable to HBV are found (Fig. S1A). HBV infection can be prevented by neonatal immunisation, which has now been introduced in 133 countries with global coverage of the full three vaccine doses estimated at 83% in 2020.[17] A modelling study estimated that 1.5 million liver cancer deaths could be avoided between 2015 and 2030 by scaling up the coverage of neonatal HBV vaccination to 80% of newborns, as well as increasing coverage of infant HBV vaccination to 90% of infants, use of peripartum antivirals to 80% of HBV-positive mothers, and population-wide testing and treatment of 80% of eligible people.[18] Many countries now have data on the first cohorts which received the HBV vaccine in infancy as they reach young adulthood; studies in Taiwan and Shanghai reported an 80% and 50% reduction in liver cancer incidence, respectively, among young adults vaccinated in infancy compared with previous or unvaccinated cohorts,[19,20] and elimination of liver cancer has been achieved in Alaskan Native children since 1999 following universal neonatal immunisation coupled with a child catch-up programme.[21]

Another major risk factor for liver cancer is chronic HCV infection which causes approximately 20% of liver cancer cases globally, and more than 50% of liver cancer cases are attributable to HCV in the most affected countries including Egypt, the US, and Pakistan[6] (Fig. S1B). There is no vaccine for HCV, but cure of chronic infection can be achieved with direct-acting antivirals (DAAs), and strategies to reduce HCV transmission can be applied worldwide.[22] A prospective study of patients with HCV infection and cirrhosis in France observed a 70% reduction in risk of liver cancer incidence after a sustained virologic response, and suggested that DAA therapy will have a substantial effect on liver cancer rates in the future.[23] This was further supported by a modelling study on patients with chronic HCV in England, which predicted an increase in liver cancer incidence unless there was a 115% increase in the number of eligible patients treated for HCV by 2018, which would have reduced the number of HCV-related liver cancer cases by 50% by 2020.[24] In response to these trends, in 2016, the World Health Organization (WHO) set a goal of reducing HBV infections by 90% and reducing HBV- and HCV-related deaths by 65% by 2030; universal health coverage, with access to HBV immunisation and affordable DAAs, is essential to achieving this goal.[25,26]

Contamination of crops by the fungi *Aspergillus flavus* also poses a threat to public health in tropical and subtropical areas that lie in the global aflatoxin belt.[27] Pre- and post-harvest strategies to decrease aflatoxin contamination including sorting crops and improving storage have been outlined,[28] but many regions in the aflatoxin belt have limited resources to implement control measures. It has been estimated that populations in sub-Saharan Africa, South-East Asia, and China have the highest burdens of liver cancer attributable to aflatoxin exposure, particularly as there is a synergistic effect between aflatoxin and HBV infection.[27] Additional causes of liver cancer must also be incorporated into planning for liver cancer control in various regions. For example, in Europe and North America excessive alcohol consumption was associated with an estimated 22% of liver cancer cases in 2020[8] (Fig. S1C), yet cost-effective policies exist to reduce consumption in the population.[29]

To explore the potential relationship between the development of a country and its rate of liver cancer incidence or mortality, we plotted HDI by liver cancer mortality rate and did not find a correlation. However, the current burden of liver cancer might be influenced by other demographic factors. For example, we found a strong male predominance for liver cancer across all world regions which has been reported previously and could be largely related to exposure to risk factors for liver cancer.[4] Ethnic disparities in liver cancer incidence have also been observed in studies using cancer registry data in the US, finding the highest rates among American Indians/Alaskan Natives, Hispanics, and Asians/Pacific Islanders.[4] Additional studies in three US states further disaggregated the ethnic groups and found the highest liver cancer incidence rates in California were among Vietnamese, Cambodian and Laotian groups,[30] and the most elevated liver cancer mortality rates in California, Florida, and New York were among Vietnamese, Chinese and Korean groups.[31] Furthermore, migration has likely influenced rates of liver cancer among ethnic minorities in Western countries, as observed in the US, Australia, Canada, and Western Europe, where the highest incidence rates were among migrants from high-risk countries.[31–34] In addition, increasing age is directly correlated with liver cancer incidence in most populations,[4] and population aging has already driven changes across the world, such as in Shanghai, China, where demographic changes, largely attributed to the aging population, accounted for 45% of the rise in liver cancer mortality between 1980 and 2019.[35] Based on population projections, population aging will continue to drive the global burden of liver cancer.

As a baseline for control of liver cancer, we estimated the potential future number of cases and deaths resulting from several scenarios. If current rates remain the same, we predict

the largest increases in liver cancer burden could occur in high HDI countries, including China, due to population growth and aging. The largest relative increases could occur in low HDI countries, where we predict that the number of liver cancer cases and deaths per year could double by 2040. Considering these changes, public health officials must prepare for the predicted increase in demand for resources to manage the care of patients with liver cancer throughout the cancer pathway, including improved access to palliative care. As our predictions are based on current rates and projected future populations, the impact of changes in risk factor exposure or national health programmes have not been taken into account, despite advances in HBV and HCV control. Recent successes include high immunisation coverage, testing, and treatment for HBV, and a reduction in new HCV infections in some regions, which has paralleled a rise in the number of people receiving curative treatment for HCV infections.[36] While we would expect these promising achievements to result in a lower number of liver cancer cases in the future if current HBV and HCV control efforts are maintained, liver cancer incidence has increased over time in several areas with low HBV and HCV endemicity.[3,37] This might be due to the growing obesity and diabetes epidemics[37]; thus, our baseline scenario of liver cancer predictions has possibly underestimated the future burden, if diabetes treatment and primary prevention of obesity are not addressed. Furthermore, focus on liver cancer prevention efforts must continue during and after the COVID-19 pandemic. Approximately 43% of countries that responded to the WHO Pulse survey reported disruption in HBV and HCV diagnosis and treatment during June 2020 to March 2021 due to the COVID-19 pandemic response.[38] The impact of these disruptions could reverse some of the progress made in HBV and HCV control and might also be reflected in future liver cancer rates.

Our study provides a global snapshot of the estimated burden of liver cancer in 2020 and is an essential tool for planning of liver cancer control. The GLOBOCAN estimates presented here were compiled using national data from population-based cancer registries and vital registration systems wherever possible.[9] While the estimation of rates is an extensive process using validated techniques, there are large gaps in data availability which could lead to a major underestimation of the burden of liver cancer in underrepresented populations. For example, only 15% of the world population and only 1% of the population in Africa were covered by the population-based cancer registries included in the latest volume of Cancer Incidence in Five Continents (vol. XI), a compilation of quality-assessed cancer registry data.[39] The expansion of the African Cancer Registry Network has led to more accurate estimates of cancer burden in sub-Saharan Africa which were utilised in the GLOBOCAN methods, but data are still limited in many low- and middle-income countries.[40] The Global Burden of Disease (GBD) Study has also produced estimates of liver cancer incidence and mortality up to 2019 using similar sources of cancer registry and vital registration data, but applying a different modelling method to obtain estimates in areas with less reliable or missing data.[7] GBD estimated that, globally, 534,000 liver cancer cases and 485,000 liver cancer deaths occurred in 2019.[7,41] These estimates were considerably lower than the 905,700 cases and 830,200 deaths in 2020 obtained from GLOBOCAN. At the national level, GBD estimates were much lower than GLOBOCAN for several of the countries which contributed the most cases and deaths to the global total; these included countries such as China which represented more than half of the difference between the GBD and GLOBOCAN estimates. For example, there were 187,700 liver cancer deaths in China according to GBD but 391,200 according to GLOBOCAN. Also, the crude rate of death from liver cancer in China according to GLOBOCAN was double that of GBD (27.0 *vs.*13.2 per 100,000). Two studies based on cancer registry data for China reported 422,1000 liver cancer deaths and a crude rate of 23.7 liver cancer deaths per 100,000 people in 2015.[42,43] Large differences were also noted for Vietnam where GLOBOCAN estimated 25,300 liver cancer deaths in 2020 but GBD estimated 2,400 in 2019; the GLOBOCAN crude rate of death from liver cancer was also 10-times as high as the GBD estimate for Vietnam (26.0 *vs.* 2.5 per 100,000). Such discrepancies are the result of the differing modelling methods used by both studies to estimate cancer burden as well as potential differences in the data sources and the recency of the input data. As part of their modelling of all causes of death, the GBD also redistributed unspecified causes of death to produce additional deaths from cancer.[7,41] Furthermore, the GBD methodology is based on global patterns of disease burden and uses covariates such as the prevalence of risk factors for liver cancer, *e.g.* HBsAg seroprevalence to impute missing cancer data, whereas the GLOBOCAN developers use a data-based approach and review available data for each country with respect to the local context and, if necessary, using information from neighbouring countries while ensuring that locally collected data form the basis of this process.[9] We believe that producing cancer burden estimates based as closely as possible on the collected data is a priority, and that providing support and capacity building through such programs as the Global Initiative for Cancer Registry Development (https://gicr.iarc.fr/) is of utmost importance to ensure the sustainability and improved coverage of cancer registries, which will in turn produce more accurate measures of cancer burden.

The limitations of our liver cancer burden estimates include the reported change over time in methods of diagnosing liver cancer, with some areas of the world using imaging more commonly than biopsy, which might also be related to global variation in liver cancer diagnoses.[14,44,45] In addition, the liver is a common site for metastasis so there is potential for some misclassification.[46] Also, our 2040 predictions were not based on recent changes in liver cancer incidence and mortality rates or risk factor exposures and did not take into account heterogeneity in incidence and mortality trends between countries; thus, there is substantial uncertainty around our predictions. Finally, while our study estimated the total burden of liver cancer, distinct patterns are evident when examining liver cancer by histology.[47] The major histologic types are hepatocellular carcinoma and intrahepatic cholangiocarcinoma and trends in the incidence of these histologic types differ: rates of hepatocellular carcinoma declined in high-risk countries, but increased in South-Central Asia, Europe, and North America between 1978 and 2012,[37] with evidence of a decline in the US since 2015;[48] rates of intrahepatic cholangiocarcinoma, however, increased in most countries between 1992 and 2012.[49] It is estimated that hepatocellular carcinoma makes up 80% of liver cancer diagnoses globally; thus, addressing risk factors for hepatocellular carcinoma in regions

with increasing rates would have the biggest impact on liver cancer burden.[47]

In summary, while the burden of liver cancer varies greatly, it is among the top three causes of cancer death in 46 countries, and among the top five causes of cancer death in 90 countries worldwide. Furthermore, the number of cases and deaths from liver cancer is predicted to increase by more than 50% over the next 20 years if global rates do not change, and will increase unless a 3% or greater annual decrease in rates is achieved. Liver cancer due to some major risk factors is preventable if control efforts are prioritised. While the impact of HBV and HCV elimination efforts is only beginning to be reflected in the burden of liver cancer today, increasing prevalence of other risk factors might drive future changes in liver cancer incidence. Considering these changes, public health officials must prepare for an increase in demand for resources to manage the care of patients with liver cancer throughout the cancer pathway.

Abbreviations

ASR, age-standardised rate; DAA, direct-acting antiviral; GBD, Global Burden of Disease; HDI, Human Development Index; M:F, male:female; UN, United Nations; WHO, World Health Organization.

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Conflict of interest

The authors declare no conflicts of interest.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Study concept and design: HR, IS, JF. Analysis and interpretation of data: JV, ML, JF, HR. Drafting the manuscript: HR. Critical revision of the manuscript for important intellectual content: all authors.

Data availability statement

All cancer incidence, mortality, and population estimates are available to the public through the Global Cancer Observatory (www.gco.iarc.fr).

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2022.08.021.

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Author names in bold designate shared co-first authorship

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A longitudinal study to detect hepatitis B surface and core-related antigens in chronic hepatitis B patients with hepatitis B surface antigen seroclearance using highly sensitive assays

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ABSTRACT

Background: This study aimed to evaluate the usefulness of two novel assays, namely the iTACT-hepatitis B surface antigen (iTACT-HBsAg) and iTACT-hepatitis B core-related antigen (iTACT-HBcrAg) assays, in chronic hepatitis B (CHB) patients with HBsAg seroclearance (SC) documented by standard assays.
Methods: HBsAg and HBcrAg were measured by the two iTACT-assays in 556 serial sera collected from 96 CHB patients at 7 different time points spanning from 5 years before to 10 years after SC and 120 HBsAg-negative, anti-HBc-positive individuals. As controls, 60 seronegative individuals, who were negative for HBsAg, anti-HBc and anti-HBs, were tested.
Results: Using the iTACT-assays, HBsAg was detectable in 154/418 (36.8%) samples collected after SC. HBcrAg was detectable in 78.3% and 65.9% of samples collected before and after SC, respectively. The detectability rates of both HBsAg and HBcrAg progressively decreased over time after SC. At 10 years after SC, 20.4% and 64.5% of the patients still had detectable HBsAg and HBcrAg, respectively. 66 (71%) patients had detectable HBsAg and/or HBcrAg. Among the 120 HBsAg-negative, anti-HBc-positive individuals, 11 (9.2%) and 4 (3.3%) had detectable HBsAg and HBcrAg respectively. Both HBsAg and HBcrAg were undetectable in the controls.
Conclusion: The iTACT assays detected a low level of HBsAg and/or HBcrAg in >70% of patients even at 10 years after SC, suggesting that CHB patients with SC still harbour a low level of HBV protein expression. The clinical significance of detectable viral proteins after SC with regard to disease progression and HBV reactivation deserves further investigations.

1. Introduction

Occult hepatitis B infection (OBI) is characterized by the detectability of hepatitis B virus (HBV) DNA in blood and/or liver in individuals with undetectable circulating hepatitis B surface antigen (HBsAg). OBI may be a result of either self-resolved acute hepatitis B infection or HBsAg seroclearance (SC) in chronic hepatitis B (CHB) patients. In areas where CHB is prevalent, SC may represent the majority of OBI cases. SC is identified when CHB patients with history of persistent positive HBsAg having subsequent HBsAg undetectable by conventional HBsAg assays. The pooled annual incidence rate of SC is 1.02% [1]. SC is regarded as functional cure and treatment endpoint in CHB. However, presumably due to residual viral activity, patients with SC are still at risk of hepatocellular carcinoma (HCC) [2]. HBV reactivation is often seen when they receive immunosuppressive therapy [3]. Therefore, accurate identification of OBI and careful monitoring of viral activity in OBI patients are warranted.

Besides HBsAg, hepatitis B core-related antigen (HBcrAg) is another common serological marker measured in CHB patients [4,5]. HBcrAg refers to a composite of three HBV proteins, namely the hepatitis B core antigen (HBcAg), hepatitis B e antigen (HBeAg) and a truncated HBcAg named p22cr. HBcrAg levels have been reported to correlate with

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disease activity [6,7] and covalently closed circular DNA (cccDNA) levels and activity [8,9] and associate with HCC risk in CHB patients treated with nucleos(t)ide analogues [10–12]. The lower limit of quantification (LLOQ) of the conventional HBcrAg assay is 3 log U/mL [13]. While the profile of HBcrAg in different HBsAg-positive phases in CHB patients is relatively well-studied [6,7], HBcrAg measurement in the HBsAg-negative phase is hampered by the low detectability, in which only 21% patients with SC had detectable HBcrAg [6,14]. By definition, HBsAg is undetectable in OBI patients when conventional HBsAg assays (LLOQ 0.05 IU/mL) are used. The lack of sensitive assays hinders the detection of residual HBV proteins in patients with SC.

Current "second-generation" HBsAg detection assays such as the HBsAg-HQ (Fujirebio Inc., Tokyo, Japan) and HBsAg-NEXT assays (Abbott Laboratories, Abbott Park, IL) have a LLOQ of 0.005 IU/mL, which is 10 × more sensitive than conventional assays. HBsAg is detectable in 7 – 26% of patients with SC if such sensitive assays are used [14,15]. Development of highly sensitive assays is still an unmet need for CHB serological testing especially at the disease phase of SC.

Recently, two novel assays, based on iTACT technology (stands for Immunoassay for Total Antigen including Complex via preTreatment) have been developed for HBsAg and HBcrAg detection [16,17]. For clarity, HBsAg and HBcrAg detected by the iTACT assays are referred to as iTACT-HBsAg and iTACT-HBcrAg, respectively, in this paper. The LLOQ of the iTACT-HBsAg and iTACT-HBcrAg assays are 0.0005 IU/mL and 2.1 log U/mL, respectively, which are 10 × more sensitive than the second-generation HBsAg and conventional HBcrAg assays. In a small-scale study, the iTACT-HBsAg assay has been demonstrated to be superior to the HBsAg-HQ assay, giving an increment of 16% for iTACT-HBsAg detection in samples collected from patients with SC [16]. In another study, iTACT-HBcrAg is detectable in 11/13 patients with HBV reactivation before the emergence of detectable HBV DNA [17].

In the present study, we investigated the longitudinal profile of iTACT-HBsAg and iTACT-HBcrAg in patients with SC. We primarily aimed to evaluate the performance of the iTACT-HBsAg and iTACT-HBcrAg assays using samples collected before and after SC. The secondary aim was to test whether iTACT-HBsAg and iTACT-HBcrAg could be detected in a cohort of HBsAg-negative, antibody-to-HBcAg (anti-HBc)-positive individuals.

2. Methods

2.1. Patients

This study included 96 CHB patients who presented to the Liver Clinics in the Queen Mary Hospital, Hong Kong in 1984 – 2010. They had documented evidence of detectable HBsAg for >6 months and subsequently developed spontaneous SC without receiving any antiviral treatment. They had been checked for the availability of stored serum samples at 5 and 3 years before SC, at the time of first documented SC, and 1, 3, 5 and 10 years after SC (Fig. 1). All patients had at least 4 samples available, with at least 3 samples collected after SC. Prior to SC, they had detectable HBsAg by the Elecsys HBsAg Quant II Assay (Roche Diagnostics, Indianapolis, IN) and/or the Architect HBsAg Quant II Assay (Abbott Laboratories). All of them were confirmed HBsAg-negative by these two conventional assays for at least 6 months apart during follow-up with the first incidence considered as the time of SC. Another 180 individuals recruited from a previous study were also tested [18]. Among them, 120 were HBsAg-negative and anti-HBc-positive. The remaining 60 serving as control subjects were negative for HBsAg, anti-HBc, and anti-HBs. HBsAg, anti-HBc and anti-HBs in these 180 subjects were detected by the Elecsys HBsAg, anti-HBc and anti-HBs Assays, respectively (Roche Diagnostics). This study was approved by the Institution Review Board of The University of Hong Kong and Hospital Authority Hong Kong West Cluster (UW14-583 and UW20-515).

2.2. Analytical measurements

iTACT-HBsAg, iTACT-HBcrAg and anti-HBs were detected by the iTACT-HBsAg assay, iTACT-HBcrAg assay and the Presto anti-HBs assay, respectively (Fujirebio). All three assays were measured using the automated chemiluminescence enzyme immunoassay (CLEIA)-based LUMIPULSE L2400 System (Fujirebio). The principles of the iTACT-HBsAg and iTACT-HBcrAg assays have been described previously [16,17]. Both the iTACT-HBsAg and iTACT-HBcrAg assays included a pre-treatment step (Fig. 2), which denatures and partially breaks down HBsAg/HBcAg and inactivates the respective antibodies so that they are readily detected by exogenous antibodies. The dynamic ranges of the iTACT-HBsAg and iTACT-HBcrAg assays were 0.0005 – 112.5 IU/mL and 2.1 – 7 log U/mL, respectively. HBV DNA was measured by the COBAS TaqMan HBV Test (LLOQ 20 IU/mL) (Roche Diagnostics).

2.3. Statistical analysis

Statistical analyses were performed using SPSS Statistics v27 (IBM, Armonk, NY). Continuous variables were expressed in median and interquartile range (IQR). Correlation between variables was analysed using the Spearman's Rank Correlation Test. Statistical significance was denoted by $P < 0.05$.

3. Results

3.1. CHB patients with spontaneously SC

Demographic data of the 96 patients (median age at SC: 52 years; IQR 45 – 47) are listed in Table 1. All except one patient were HBeAg-negative at 5 years prior to SC. HBV DNA data were available in 69 patients, of whom 68%, 43% and 7% patients had detectable HBV DNA at 5 years before (median: 130 IU/mL; IQR <20 – 686), 3 years before (median <20 IU/mL;IQR <20 – 126) and at the time of SC, respectively. HBV DNA was undetectable in all samples collected after SC (Fig. 3). Majority of patients (79 – 84% before SC; 94% at the time of SC, and 89 – 95% after SC) had normal ALT (<40 U/L) (Fig. 3B). Transient elastography measurement showed that 33/38 (87%) patients had fibrosis stage F0-F2.

A total of 556 samples (138 before and 418 after SC) were tested. All

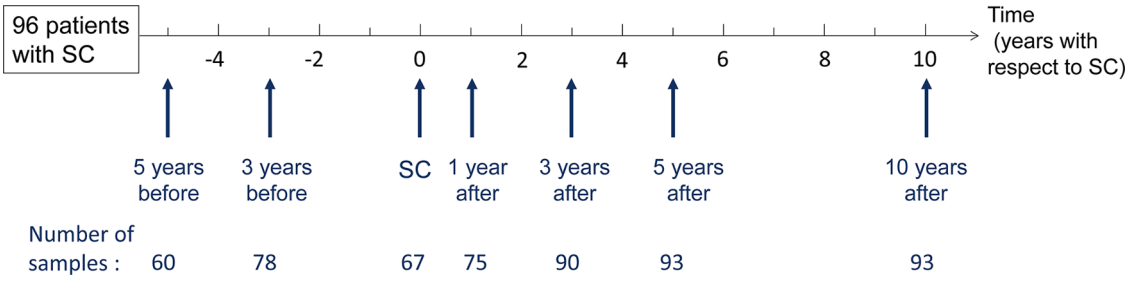


Fig. 1. Disposition of patient samples with respect to HBsAg seroclearance (SC).

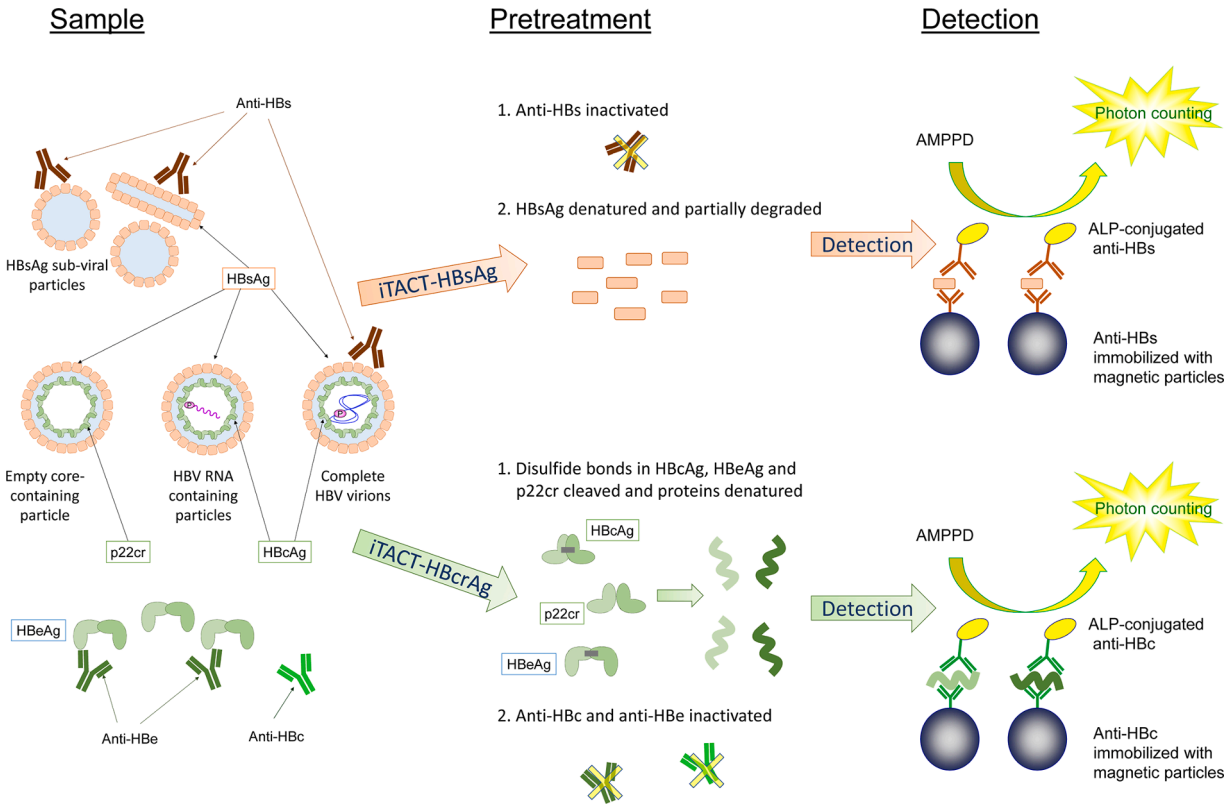


Fig. 2. Principles of the iTACT-HBsAg and iTACT-HBcrAg assays. The inclusion of the pre-treatment step denatures the HBV proteins and inactivates respective antibodies. AMPPD; 3-(2'-spiroadamantan)–4-methoxy-4-(3'-phosphoryloxy) phenyl–1,2-dioxetane disodium salt; ALP, alkaline phosphatase.

Table 1
Demographic data of the 96 patients with HBsAg seroclearance.

Patient characteristics [a]	
Gender (M: F)	72: 24
Age at first presentation, years	44 (35 – 50)
No. of HBeAg-positive patients at first presentation (%)[b]	3 (3.2%)
Age at HBeAg seroconversion, years	39 (36 – 41)
Age at HBsAg seroclearance, years	52 (45 – 57)
Alanine transaminase at HBsAg seroclearance, U/L	21 (18 – 29)
HBV genotypes	
B	7
C	13
Not determined	72
Fibrosis Stage [c,d]	
F0 – F1	19
F2	14
F3	2
F4	3

[a] Continuous variables are expressed as median (interquartile range)
[b] At the time of first sample (5 years before HBsAg seroclearance), two patients had HBeAg-seroconversion; only one patient was HBeAg-positive.
[c] Based on transient elastography score and criteria according to the EASL guidelines [30].
[d] 38 patients had available transient elastography score during the sample collection period (5 years before to 10 years after SC).

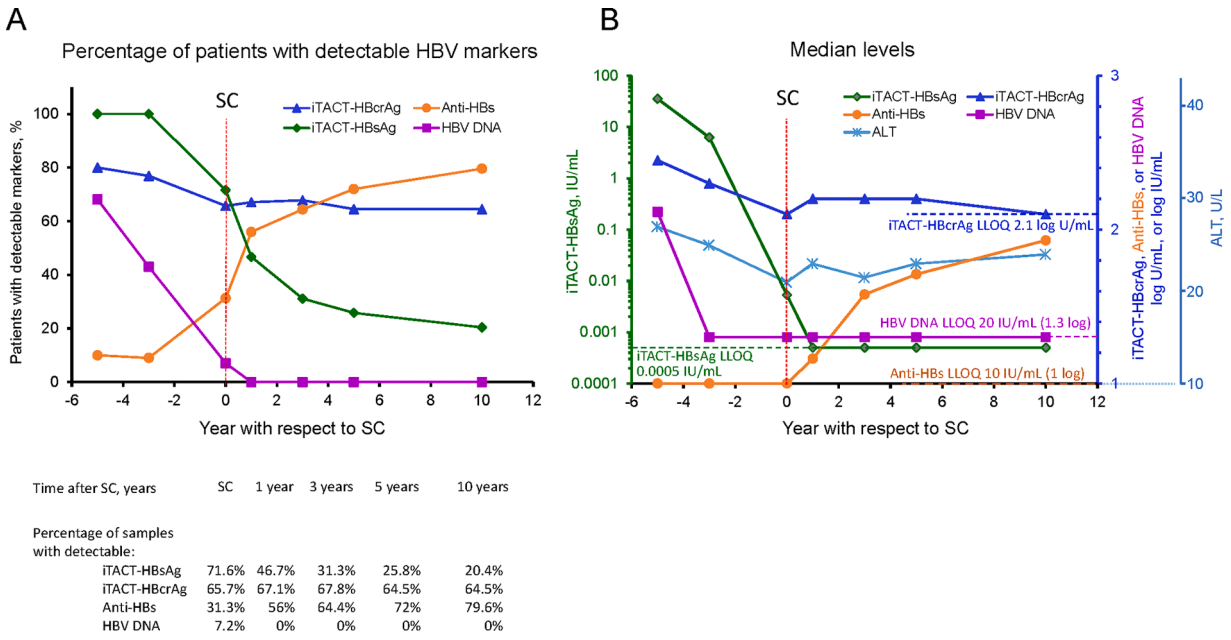
samples collected before SC had detectable iTACT-HBsAg (median 11.4 IU/mL; IQR: 1.7 – 77.2 IU/mL). iTACT-HBcrAg was detectable in 108/138 (78.3%) samples collected before SC (median: 2.4 log U/mL; IQR: <2.1 – 2.8 log U/mL). Among the 418 post-SC samples, 154 (36.8%) had detectable iTACT-HBsAg, of which 68 (44.2%) had levels <0.005 IU/mL (LLOQ of the second-generation HBsAg assays) and 274 (65.9%) had detectable iTACT-HBcrAg, of which 251 (92%) levels <3 log U/mL (LLOQ of the conventional HBcrAg assay). 13/138 (9.4%) of the pre-SC samples and 262/418 (62.7%) of the post-SC samples had detectable anti-HBs. 68 (26%) anti-HBs-positive post-SC samples had detectable iTACT-HBsAg. iTACT-HBsAg correlated weakly with iTACT-HBcrAg ($\rho = 0.247$, $P < 0.0001$).

Profiles of the three serological markers are shown in Fig. 3. At the time of SC, 71.6% of the patients had detectable iTACT-HBsAg (Fig. 3A). The detectability of iTACT-HBsAg decreased over time after SC, with 46.7%, 31.1%, 25.8% and 20.4% of patients having detectable iTACT-HBsAg at year 1, 3, 5 and 10 after SC, respectively. iTACT-HBsAg levels also declined through time (Fig. 3B). Median iTACT-HBsAg titre at 5 years before SC was 35.55 IU/mL (IQR 6.3 – >112.5), and it declined to 6.26 IU/mL (IQR 0.73 – 24) at 3 years before SC and 0.0053 IU/mL (IQR <0.0005 – 0.07) at the time of SC. At 10 years after SC, 19 patients had detectable iTACT-HBsAg (range: 0.00051 – 0.04 IU/mL). 31% of patients developed detectable anti-HBs at the time of SC. The percentage of anti-HBs-positive patients increased to 80% at 10 years after SC (median anti-HBs: 85.2 IU/L; IQR 22 – 474) (Fig. 3B).

At 5 years before SC, 80% of the patients had detectable iTACT-HBcrAg (median 2.45 log U/mL; IQR 2.1 – 3). The detectable rate decreased to 66% at the time of SC and remained steady at 65-68 % thereafter (Fig. 3A). iTACT-HBcrAg did not fluctuate greatly after SC, with median levels of 2.1 – 2.2 log U/mL (Fig. 3B).

Of the 96 patients, 10 (10.4%) had detectable iTACT-HBsAg and iTACT-HBcrAg at all time points after SC. 85 (88.5%) had detectable iTACT-HBsAg and/or iTACT-HBcrAg at least one time point after SC. Even at 10 years after SC, 66 (71%) patients still had either one or both of iTACT-HBsAg and iTACT-HBcrAg detectable, of whom 7 (11%) patients had iTACT-HBsAg/iTACT-HBcrAg levels above the LLOQ of the older generation assays (6 had iTACT-HBsAg >0.005 IU/mL and 1 had iTACT-HBcrAg >3 log U/mL).

Two male patients, with SC at age 57 and 60 years, developed HCC at 13 and 8 years after SC, respectively. One had detectable iTACT-HBsAg and undetectable iTACT-HBcrAg at the time of SC, and undetectable iTACT-HBsAg and iTACT-HBcrAg at all time points thereafter. The other



Time after SC, years	SC	1 year	3 years	5 years	10 years
Percentage of samples with detectable:					
iTACT-HBsAg	71.6%	46.7%	31.3%	25.8%	20.4%
iTACT-HBcrAg	65.7%	67.1%	67.8%	64.5%	64.5%
Anti-HBs	31.3%	56%	64.4%	72%	79.6%
HBV DNA	7.2%	0%	0%	0%	0%

Fig. 3. Detectability (A) and levels (B) of iTACT-HBsAg, iTACT-HBcrAg, anti-HBs and HBV DNA at various time points before and after HBsAg seroclearance (SC). The lower limit of quantification (LLOQ) of the iTACT-HBsAg, iTACT-HBcrAg, anti-HBs and HBV DNA assays are 0.0005 IU/mL, 2.1 log U/mL and 10 IU/L (1 log IU/L) and 20 IU/mL (1.3 log IU/mL), respectively, and are shown as the horizontal dotted lines. ALT levels were also shown in (B).

HCC patient had undetectable iTACT-HBsAg but detectable iTACT-HBcrAg at all time points after SC. Both patients had undetectable HBV DNA and normal ALT after SC.

3.2. *HBsAg-negative, anti-HBc-positive individuals*

We measured iTACT-HBsAg and iTACT-HBcrAg in 120 HBsAg-negative, anti-HBc-positive individuals (60 males and 60 females; mean age: 51 years). Anti-HBs was detectable in 103 (86%) of them (median 163 IU/L; IQR 25 - 595). 11 (9.2%) and 4 (3.3%) individuals had detectable iTACT-HBsAg and iTACT-HBcrAg, respectively, and 12 (10%) had either one or both markers detectable. For those with detectable levels, iTACT-HBsAg and iTACT-HBcrAg ranged from 0.00051 to 0.05 IU/mL and 2.1 to 2.3 log U/mL, respectively. 31 out of 120 of the subjects had reported history of HBV vaccination, none of whom had detectable iTACT-HBcrAg, and only 1 (3.2%) had detectable iTACT-HBsAg.

3.3. *HBsAg-negative, anti-HBc-negative, anti-HBs-negative controls*

As controls, 60 individuals (28 males and 32 females; mean age: 52 years) who were negative for HBsAg, anti-HBc and anti-HBs were subjected to iTACT-HBsAg and iTACT-HBcrAg measurements. All 60 individuals had undetectable iTACT-HBsAg and iTACT-HBcrAg.

4. Discussion

The present study is a unique and longitudinal study with a relatively large cohort of patients with SC with serial samples spanning from 5 years before to 10 years after SC. We adopted novel assays utilizing a new technology perform (i.e. iTACT) to measure HBsAg and HBcrAg in a CHB population with SC who have an extremely low circulating viral antigens. The pre-treatment step in the assays dissociates the corresponding antigen-antibody complexes and simultaneously denatures HBsAg/HBcAg for easier detection. This results in an enhanced sensitivity of approximately 10-fold when compared with the second-generation HBsAg assays and the conventional HBcrAg assay. The high specificity of the two assays were demonstrated in that both iTACT-HBsAg and iTACT-HBcrAg were undetectable in the "all negative" (HBsAg-, anti-HBc- and anti-HBs-negative) control subjects.

In this study, we found that even at 10 years after SC, 66 (71%) patients still had detectable iTACT-HBsAg and/or iTACT-HBcrAg. Judging by their titres, we estimated that only 7 patients would have detectable HBsAg/HBcrAg at year 10 if older assays were used. The present finding suggests that, even after a long period of SC, majority of patients still had a very low level of viral transcriptional activity, the detection of which was greatly improved by the use of the two iTACT assays. The expression of HBV proteins may be from cccDNA and/or the integrated form of HBV DNA, both of which have been reported to be detectable in the liver of patients with SC or OBI [2,19-21]. Due to the pattern of HBV integration, HBsAg can be expressed from both cccDNA and integrated HBV DNA, while HBcrAg is mostly expressed from cccDNA. Therefore, theoretically, HBsAg is expected to be more readily detectable than HBcrAg in patients with SC. However, for unknown reasons, we found that iTACT-HBcrAg had a higher detection rate than iTACT-HBsAg after SC. It could be envisaged that investigating whether transcription activities from the precore/core promoters are higher than that of the preS/S promoters after SC and whether iTACT-HBcrAg and iTACT-HBsAg levels are associated with the levels of cccDNA and HBV integration after SC could provide more insights into viral activities after SC. Another possible reason may be due to intrinsic differences in the performance of the two iTACT assays.

This study also employed the iTACT assays in individuals from the general public in a geographical area that is endemic for CHB and thus high seroprevalence of anti-HBc-positivity [18] and found that only 10% of the 120 HBsAg-negative, anti-HBc-positive individuals had detectable iTACT-HBsAg and/or iTACT-HBcrAg. Although their anti-HBc-positivity suggested that they should have previous exposure to HBV, this study is limited in that data on their prior HBsAg history and confirmatory serological tests (such as anti-HBe) were not available to determine their OBI status. While the possibility of their HBsAg and HBcrAg expressions being too low to be detected by the iTACT assays cannot be ruled out, the relatively low iTACT-HBsAg/iTACT-HBcrAg detection rate suggested that the majority of these individuals are likely not having OBI. This is exemplified by that vast majority (30/31) of HBV-vaccinated individuals, who are prevented from establishing chronicity upon HBV

exposure [22], did not have detectable iTACT-HBsAg/iTACT-HBcrAg.

The detection of low levels of HBsAg and HBcrAg in OBI patients is especially useful in preventing HBV reactivation [23–25]. Current major guidelines suggest that antiviral treatment could be stopped after sustained SC [26–28]. It remains to be studied whether low iTACT-HBsAg and iTACT-HBcrAg levels are predictive of the likelihood of relapse in patients who stopped antiviral treatment after SC.

HBcrAg levels have been reported to associate with HCC in CHB patients [10,29]. In this study, we found that one patient who developed HCC after SC had persistently detectable iTACT-HBcrAg, suggesting that a low iTACT-HBcrAg level may predict HCC risk after SC. However, this study is limited by the small number of HCC patients and its retrospective nature. The association between HCC and the detectability/-levels of iTACT-HBcrAg and iTACT-HBsAg after SC deserves to be studied in a prospective cohort with a longer follow-up. Besides, this study is limited by that other serological measurements such as quantitative anti-HBc and anti-HBe are not available, precluding a comprehensive analysis of HBV activities in these patients.

5. Conclusion

We detected a low level of iTACT-HBsAg in >35% and iTACT-HBcrAg in >65% of the post-SC samples. Even at 10 years after SC, >70% of patients still had detectable iTACT-HBsAg and/or iTACT-HBcrAg, demonstrating the presence of viral protein expression in a notable proportion of patients with SC. The clinical significance and the predictive values of the low levels of iTACT-HBsAg and iTACT-HBcrAg deserve further investigation.

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Author contributions

Conception and design: D Wong and MF Yuen; drafting of manuscript: D Wong; acquisition, analysis and interpretation of data: D Wong, T Inoue, and Y Tanaka; critical revision of the manuscript: T Inoue, LY Mak, RW Hui, J Fung, KS Cheung, and Y Tanaka; study supervision: Y Tanaka and MF Yuen.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The iTACT-assays used in this study was supported by Fujirebio Inc. D Wong received speaker's fee from Abbott Laboratories and meetings and/or travel support from Gilead Sciences. T Inoue received research funding from Fujirebio, Inc. and Sysmex Corporation. J Fung is an advisory board member of Gilead Sciences. WK Seto received speaker's fees from AstraZeneca and Mylan, is an advisory board member of Abbott, is an advisory board member and received speaker's fees from AbbVie, and is an advisory board member, received speaker's fees and researching funding from Gilead Sciences. Y Tanaka received research funding from FUJIFILM Corporation, Janssen Pharmaceutical K.K., Gilead Sciences, Board of Trustees of the Leland Stanford Junior University, GlaxoSmithKline PLC, Fujirebio Incorporation and Sysmex Corporation and received speaker's fees from Fujirebio, Inc., Gilead Sciences and GlaxoSmithKline PLC. MF Yuen received research funding from Assembly Biosciences, Arrowhead Pharmaceuticals, Fujirebio Incorporation, Sysmex Corporation, and is an advisory board member and/or received research funding from AbbVie, Aligos therapeutics, Arbutus Biopharma, Bristol Myer Squibb, Dicerna Pharmaceuticals, Finch Therapeutics, GlaxoSmithKline, Gilead Sciences, Janssen, Merck Sharp and Dohme, Clear B Therapeutics, Springbank Pharmaceuticals, Roche. The rest of the authors have nothing to disclose.

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Low Performance of Hepatitis Delta Virus Testing Among 2 National Cohorts of Chronic Hepatitis B Patients in the United States

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INTRODUCTION: **The purpose of this study was to evaluate hepatitis delta virus (HDV) testing patterns among US adults with chronic hepatitis B (CHB).**

METHODS: **HDV testing was evaluated among CHB patients using Quest Diagnostics (2016–2020) and Veterans Affairs (2010–2020) data.**

RESULTS: **Among 157,333 CHB patients (Quest), 6.7% received HDV testing, among which 2.2% were positive. HDV testing was higher in male patients, younger individuals, and patients with advanced liver disease. Among 12,002 CHB patients (Veterans Affairs), 19.7% received HDV testing, among which 3.1% were positive. HDV testing was higher in younger individuals and Asians.**

DISCUSSION: **Low HDV testing was observed among 2 large US cohorts of adults with CHB.**

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INTRODUCTION

Hepatitis delta virus (HDV) infection is associated with more aggressive disease progression in patients with chronic hepatitis B (CHB) infection (1–7). Suboptimal awareness and nonroutine HDV testing among CHB patients persists. Recent studies estimate the global HDV prevalence to be approximately 12 million (8). Studies evaluating HDV prevalence in the United States are limited, and lack of an effective national CHB surveillance system, compounded by suboptimal HDV testing and nonexistent reporting systems for HDV, contributes to uncertainly about HDV burden. Data from Stockdale et al (8,9) reported an HDV prevalence of 5.9% among US adults with CHB, translating to an estimated 142,000 adults with HDV. However, few large studies exist evaluating HDV testing patterns among US adults with CHB.

METHODS

Adults with CHB were identified using 2016–2020 Quest Diagnostics clinical laboratory data and 2010–2020 national Veterans Affairs (VA) data, based on 2 positive results of any combination of hepatitis B virus (HBV) surface antigen, HBV e antigen, or HBV DNA, performed at least 6 months apart, or 1 positive aforementioned HBV test and 1 *International Classification of Diseases, Ninth/Tenth Revision* code for chronic HBV.

HDV tests included HDV total antibody (HDV Ab), HDV IgM, and HDV RNA in the Quest cohort and included HDV Ab, HDV antigen (HDV Ag), and HDV RNA in the VA cohort. Comparisons of HDV testing (with any HDV test) between groups used χ^2 tests, and adjusted multivariable logistic regression analyses were performed to evaluate predictors of HDV testing. HDV testing patterns and HDV test results were stratified by variables available in the data set. Race/ethnicity in the VA was based on self-report and in the Quest cohort was determined by linking patient zip code data to estimated race/ethnicity proportions using the 2019 5-year American Community Survey Data from the US Census Bureau. Statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC). This study was approved by the Stanford University Institutional Review Board.

RESULTS

Among 157,333 CHB patients in the Quest cohort, 6.7% received HDV testing. The mean time from CHB diagnosis to HDV testing was 167 days (SD 321), which was similar in HDV-positive (185 days) and HDV-negative (166 days) patients. Patient characteristics were stratified by whether HDV testing was performed and HDV test results (Table 1). We observed higher rates of HDV testing in men vs women, younger patients, and patients with fibrosis-4 (FIB-4) score >3.25 (Figure 1). HDV testing rates increased from 4.7% in 2016 to 8.9% in 2020, $P < 0.02$ (Figure 2). On multivariable analyses, higher odds of HDV testing was observed in men vs women (odds ratio [OR] 1.21, 95% confidence interval [CI] 1.15–1.27), among age 18–39 years vs 60 years and

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Table 1. Characteristics of the CHB cohort among both the Quest and VA data sets

	Not tested for HDV	Tested for HDV	HDV-positive	HDV-negative
Quest CHB cohort Total (n = 157,333)				
Male (n = 79,784)	50.3%	55.2%	65.0%	45.0%
Female (n = 77,401)	49.6%	44.8%	35.0%	54.9%
Age 18–39 (n = 46,477)	28.0%	33.8%	33.6%	33.8%
Age 40–59 (n = 73,916)	48.2%	46.3%	42.1%	46.3%
Age 60+ (n = 35,460)	23.1%	19.4%	23.6%	19.3%
Non-Hispanic White (n = 63,165)	38.3%	40.0%	43.2%	40.0%
Black/African American (n = 18,457)	10.9%	13.3%	12.9%	13.3%
Hispanic (n = 37,471)	25.8%	26.5%	24.5%	26.5%
Asian (n = 31,424)	21.9%	16.8%	15.8%	16.8%
Other (n = 5,131)	3.1%	3.4%	3.6%	3.4%
ALT (mean [SD])	34.2 (78.2)	58.0 (163.2)	91.6 (158.3)	57.2 (163.3)
AST (mean [SD])	28.8 (51.4)	43.9 (109.2)	71.6 (141.4)	43.3 (108.3)
Platelets (mean [SD])	219.6 (62.3)	216.4 (67.6)	177.5 (74.2)	217.2 (67.2)
VA CHB cohort Total (n = 12,002)				
Male (n = 11,268)	93.9%	93.9%	97.1%	93.7%
Female (n = 734)	6.1%	6.1%	2.9%	6.3%
Age 18–39 (n = 718)	10.6%	15.3%	22.9%	15.8%
Age 40–59 (n = 3,545)	48.2%	47.9%	42.9%	47.5%
Age 60+ (n = 7,739)	41.3%	36.8%	34.3%	36.7%
Non-Hispanic White (n = 4,696)	41.0%	39.2%	32.9%	40.5%
Black/African American (n = 5,003)	41.5%	39.3%	48.6%	36.9%
Hispanic (n = 218)	2.8%	3.6%	5.7%	3.8%
Asian (n = 1,246)	9.6%	12.8%	8.6%	13.6%
Other (n = 809)	5.3%	5.2%	4.3%	5.3%
ALT (mean [SD])	50.0 (50.2)	60.5 (62.5)	64.0 (44.6)	60.7 (63.3)
AST (mean [SD])	47.8 (49.4)	52.5 (52.2)	53.3 (33.9)	51.9 (53.6)
Platelets (mean [SD])	201.1 (71.4)	199.9 (69.2)	172.7 (63.3)	199.2 (68.2)

ALT, alanine transaminase; AST, aspartate transaminase; CHB, chronic hepatitis B; HDV, hepatitis delta virus; VA, veterans affairs.

older (OR 1.64, 95% CI 1.52–1.76), and in FIB-4 >3.25 vs FIB-4 <3.25 (OR 2.30, 95% CI 2.08–2.56). Among CHB patients tested for HDV, 2.2% (95% CI 1.9–2.6) were positive.

Among 12,002 CHB patients in the VA cohort, 19.7% received HDV testing. The mean time from CHB diagnosis to HDV testing was 928 days (SD 1107), which was similar in HDV-positive (982 days) and HDV-negative (930 days) patients. Patient characteristics by HDV testing and HDV test results are presented in Table 1. HDV testing was higher in younger patients, Asians, and Hispanics (Figure 1). HDV testing increased from 15.4% in 2011–2012 to 28.1% in 2019–2020, $P < 0.05$ (Figure 2). On multivariable analyses, higher odds of HDV testing was observed in Asian vs non-Hispanic White (OR 1.23, 95% CI 1.05–1.45) and among age 18–39 years vs 60 years and older (OR 1.53, 95% CI 1.31–1.78). Among CHB patients tested for HDV, 3.1% (95% CI 2.4–3.8) were positive.

DISCUSSION

Our findings are similar to existing studies in smaller US cohorts reporting low rates of HDV testing among CHB patients (4,10–12). Gish et al (12) retrospectively evaluated 1191 CHB patients at a single center from 2002 to 2007 and observed that 499 patients underwent HDV testing, among whom 42 (8%) were found to be HDV-positive. Safaie et al (11) also retrospectively evaluated single-center data from 2012 to 2016. Among 1,007 patients with CHB, 121 (12%) were tested for HDV using HDV Ab, and of those tested, 4 were positive (3.3%). Kushner et al (4) retrospectively evaluated VA data from 1999 to 2013, and among 25,603 patients with positive HBsAg, 8.5% were tested for HDV Ab, among which 3.4% were positive. Low rates of HDV testing likely reflect multiple challenges ranging from lack of provider awareness, limited availability of HDV testing, limited HDV treatment options, and lack of clarity on which individuals to screen.

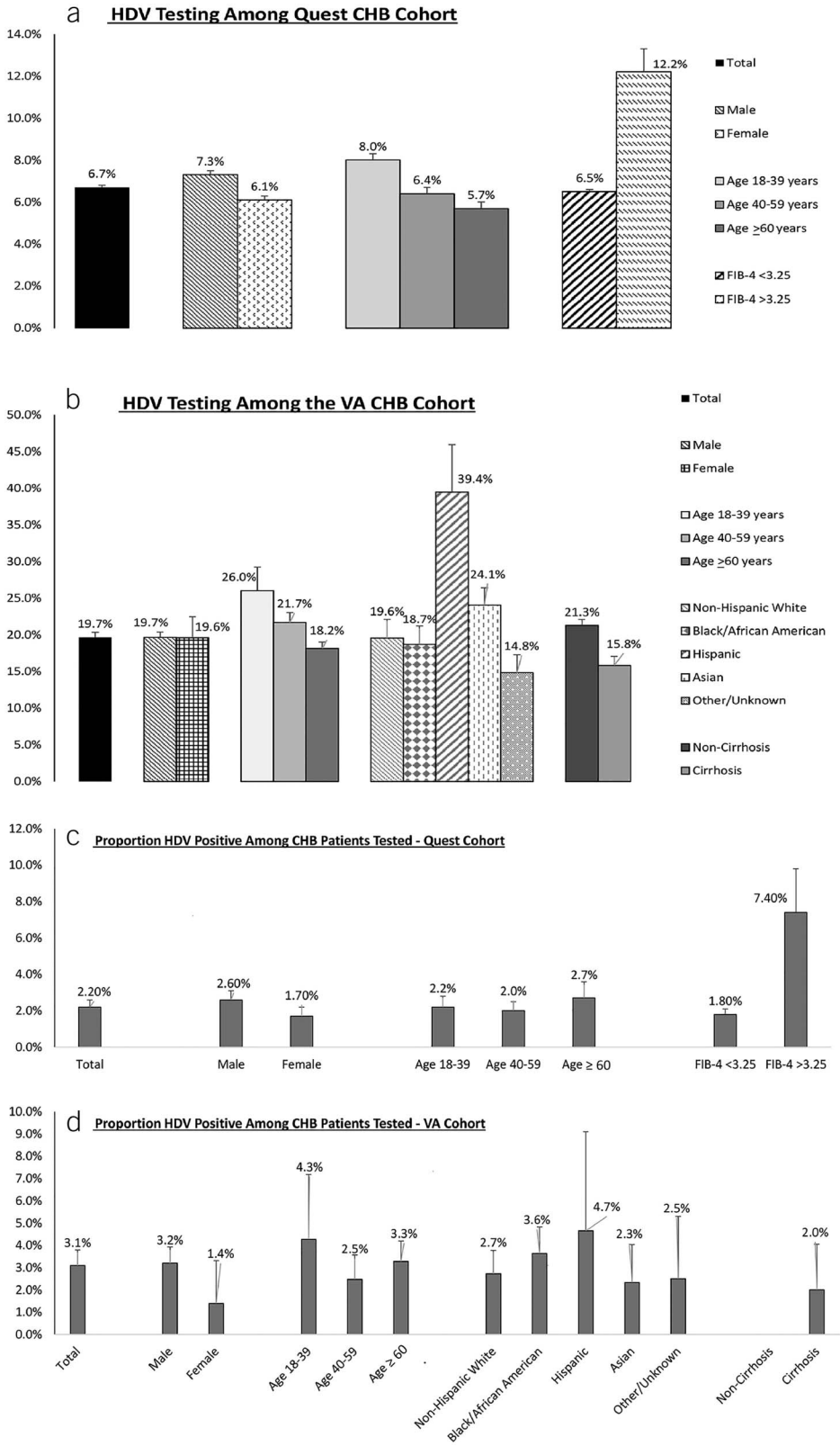

Figure 1. Proportion of CHB patients who received HDV testing in the (**a**) Quest and (**b**) VA cohorts and proportion of HDV-positive patients among CHB patients tested in the (**c**) Quest and (**d**) VA cohorts. FIB-4, fibrosis-4; HDV, hepatitis delta virus; VA, Veterans Affairs.

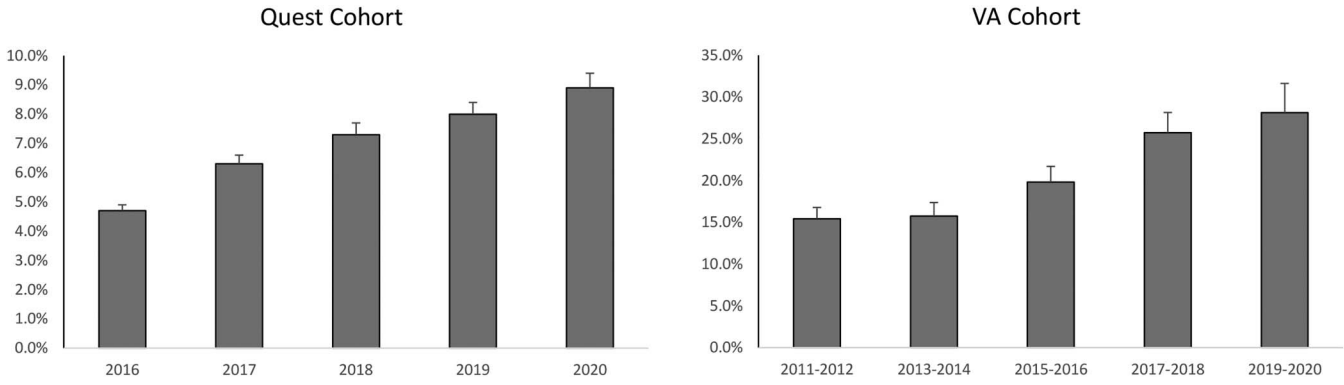

Figure 2. Hepatitis delta virus testing over time among both the Quest and VA CHB cohorts. VA, Veterans Affairs.

The HDV prevalence in this study is lower than existing estimates (8). Accurate estimates of overall HDV prevalence in the United States have been limited by few large studies or studies that have mostly involved single-center cohorts or targeted high-risk populations. Given the observational nature of our study, it was not possible to determine the reasons for HDV testing, and it is likely that HDV testing was conducted in a targeted fashion with variability between providers. Thus, if HDV testing was performed more broadly, it is possible that the HDV prevalence may be even lower.

Despite using 2 large US cohorts of adults with CHB, limitations need to be considered when interpreting these data. As previously mentioned, reasons for HDV testing could not be evaluated, and thus, our study did not determine appropriateness of HDV testing. There may also be limitations of HDV assays in detecting genotypes outside 1 and 3. Although we were able to capture race/ethnicity-specific HDV testing patterns, we were not able to directly evaluate race/ethnicity HDV testing patterns in the Quest cohort because the low rates of testing (6.7%) limit the reliability of race/ethnicity data that were estimated based on linking patient zip codes using US Census Bureau data. The 2 study cohorts may underrepresent people who are incarcerated or homeless, who may have higher rates of both CHB and HDV infections.

In conclusion, among 2 national cohorts of CHB patients, we observed low rates of HDV testing of 6.7% and 19.7%, and among patients who were tested, proportions with positive HDV test results were 2.2% and 3.1%, respectively. Raising HDV awareness, improving quality and availability of HDV diagnostics, and updating HDV testing recommendations to provide more clarity and consistency are needed.

CONFLICTS OF INTEREST

Guarantor of the article: Robert J. Wong, MD.

Specific author contributions: All authors: study concept and design; analysis and interpretation of the data; drafting of the manuscript; and critical revision of the manuscript for important intellectual content. J.K.N., C.C., and Z.Y.: acquisition of data and statistical analyses. R.J.W.: study supervision.

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