Risk of liver cancer in Hepatitis Delta virus infection

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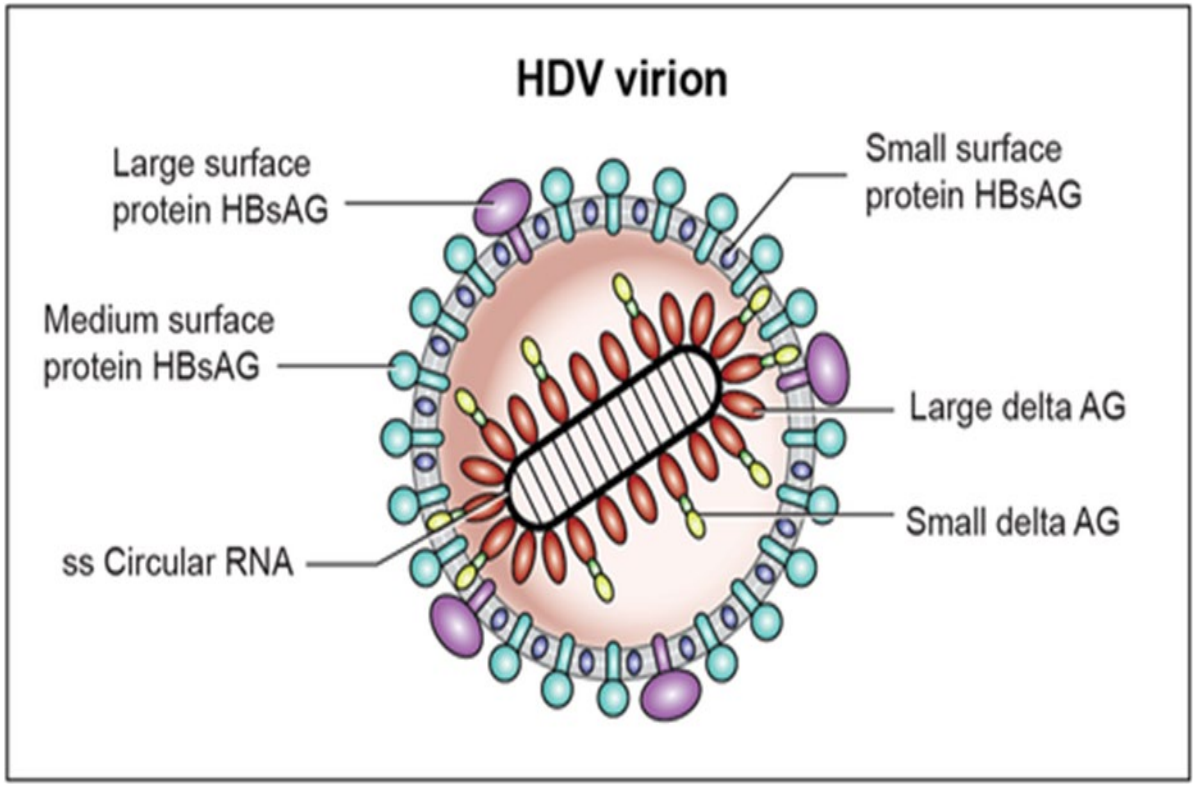
Disclosure

- Gilead Nordic fellowship 2019, 2021
- Funds from Region Stockholm (ALF grant)
- Presentation not designated to provide medical advice, please refer to your health care provider for individual management.

HDV the discovery

- Discovered by Dr. Mario Rizzetto in 1977 in a series of patients presenting with severe hepatitis.

- Single stranded RNA virus depends on HBV for propagation.
- Replication in the hepatocyte nucleus.
- Uses host RNA polymerase.
- 8 genotypes (1 and 3 severe course)



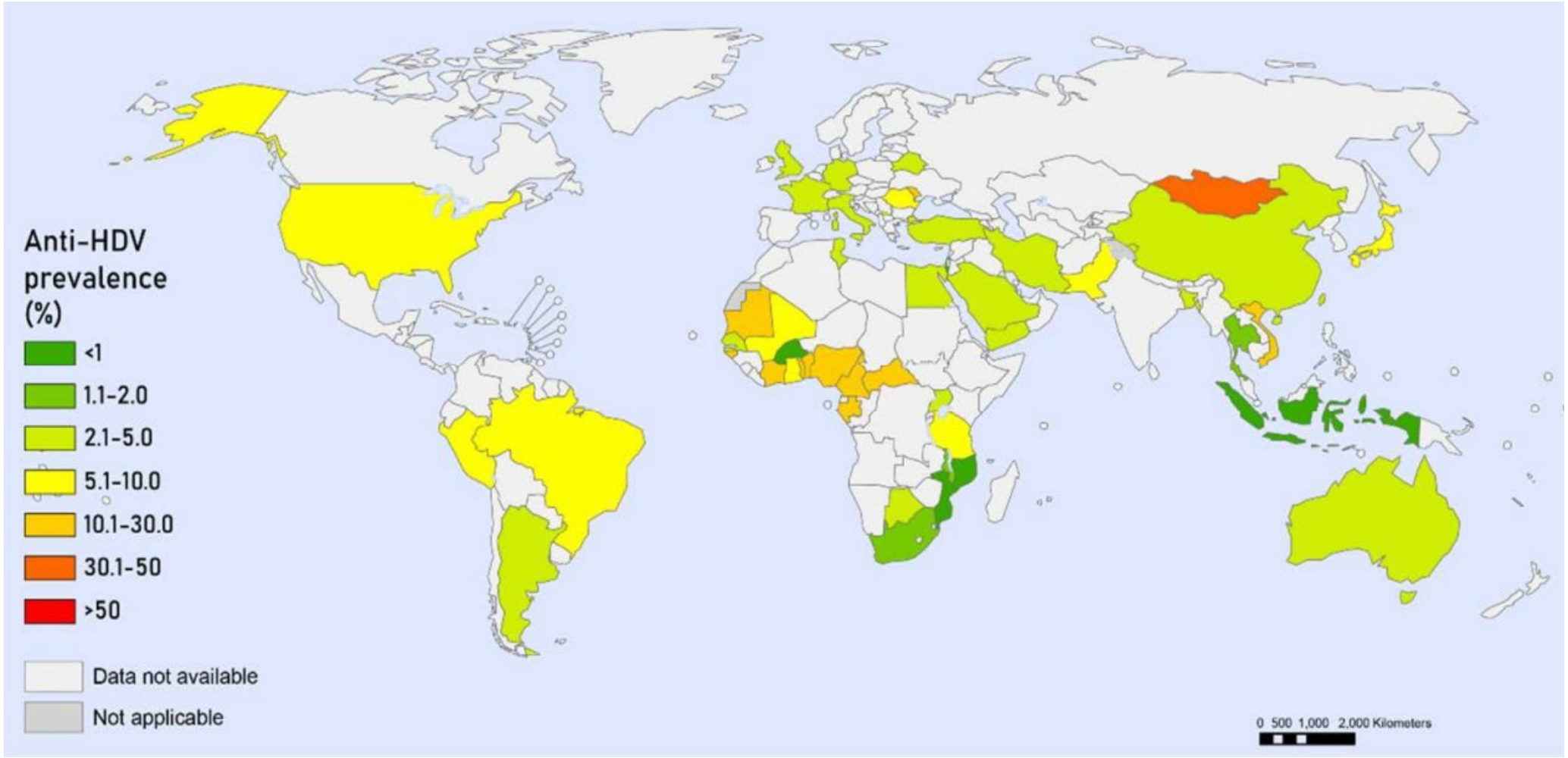
Yardeni et al, Journal of Viral Hepatitis 2022

The “Unusual suspect” in viral hepatides

- The least common among viral hepatides.
- Prevalence is debated (5%-15%) of chronic HBV carriers are living with HDV infection.
- No consensus among meta-analyses about the world prevalence spanning from 12-70 million.

Not a vanishing disease

~ 15-20 million persons are living with chronic HDV *(least estimates)*



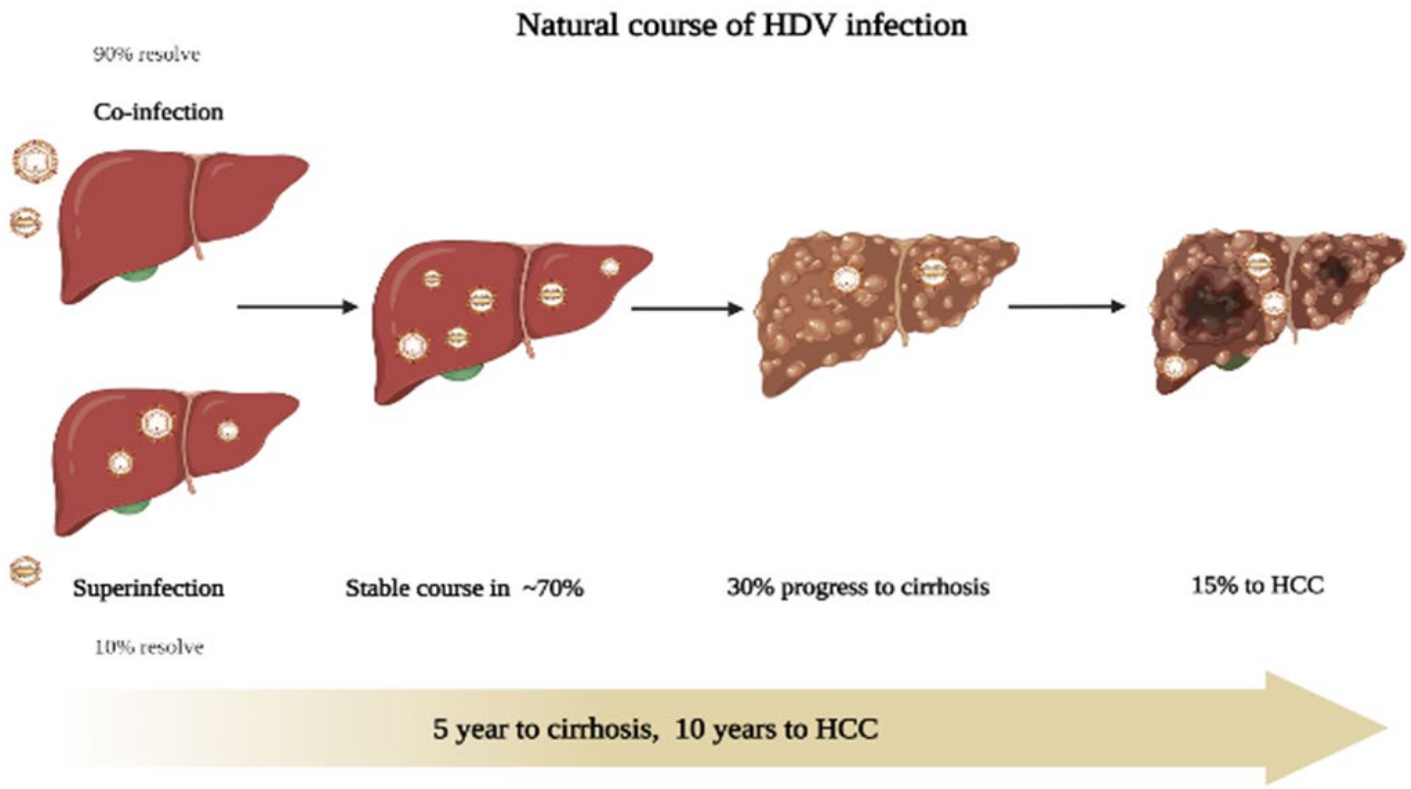
Alexander St. et al., J Hepatology 2020.

What the eye doesn't see and the mind doesn't know, doesn't exist”

- No reflex screening even in high-income settings.
- Low awareness (orphan disease).
- Discrepancy among guidelines for screening (AASLD, EASL, APASL..)
- Not all patients tested for HDV RNA (quantitative tests) especially in low-income settings.

Cumulative evidence

- Aggressive chronic course based on studies conducted in middle- and high-income settings
- Scarse longitudinal studies in endemic regions.



At HDV diagnosis

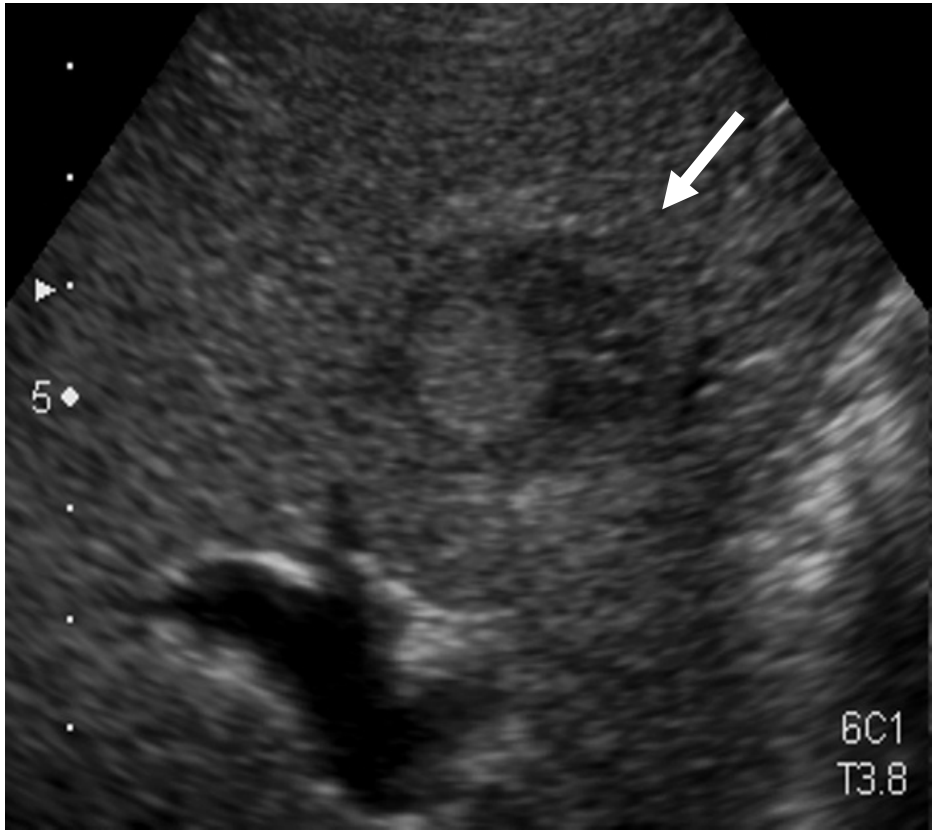
- 1 in 3 patients has already liver cirrhosis at diagnosis.
- 2 in 3 patients have detected HDV RNA.
- HDV RNA persistence is associated with worse disease course regardless of ethnicity or genotypes.
- Genotype 5 have a favorable outcome.

Liver cirrhosis is silent *until late*

- Predictors for faster progression to cirrhosis are still ill defined (HDV RNA replication, genotypes 1 and 3, comorbidities like DM2, alcohol overconsumption, metabolic syndrome)
- No difference between males and females into progression towards cirrhosis, HCC is higher among male patients.
- Older age tend to increase the risk of a worse outcome.

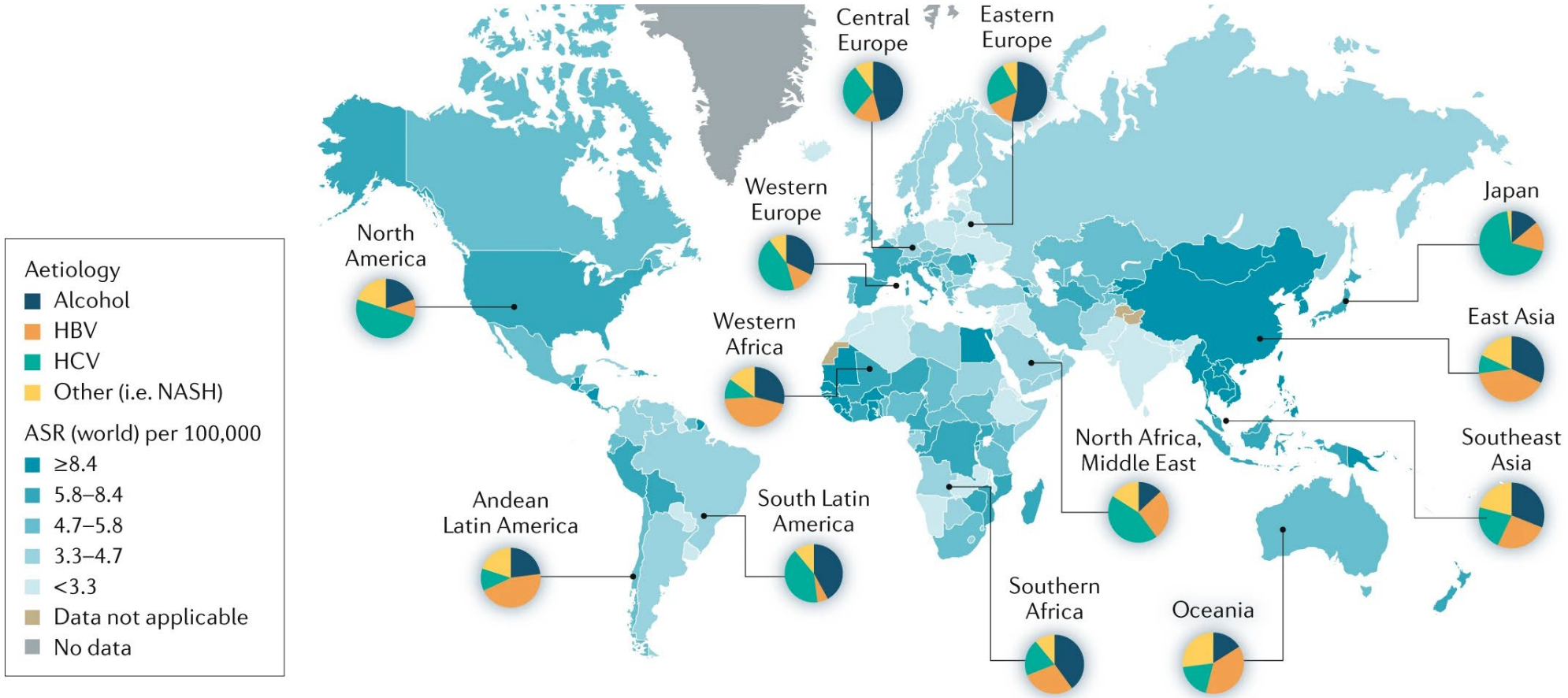
Liver cancer

- In 2020, the 6th most common cancer.
- The 2nd leading cancer-related mortality among adult males.
- 80-90% develops in a background of liver cirrhosis
- 50% attributed to HBV infection.
- Most common type (90%) is hepatocellular carcinoma.



Cancer today, https://gco.iarc.fr/

- HBV is an oncogenic virus responsible for ~50% of world's HCC per 2020 estimates.
- Can occur in liver without cirrhosis.
- Effective treatment markedly decreased the risk for HCC



Research Article
Viral Hepatitis

JOURNAL OF HEPATOLOGY

Chronic hepatitis D and hepatocellular carcinoma: A systematic review and meta-analysis of observational studies

Dulce Alfaiate[1,†], Sophie Clément[2], Diana Gomes[1], Nicolas Goossens[3,‡], Francesco Negro[2,3,*,‡]

[1]Department of Pathology and Immunology, University of Geneva, Geneva, Switzerland; [2]Division of Clinical Pathology, Geneva University Hospitals, Geneva, Switzerland; [3]Division of Gastroenterology and Hepatology, Geneva University Hospitals, Geneva, Switzerland

The Journal of Infectious Diseases
MAJOR ARTICLE

IDSA Infectious Diseases Society of America
hivma hiv medicine association
OXFORD

Estimating the Global Prevalence, Disease Progression, and Clinical Outcome of Hepatitis Delta Virus Infection

Zhijiang Miao,[1] Shaoshi Zhang,[1] Xumin Ou,[1] Shan Li,[1,2] Zhongren Ma,[3] Wenshi Wang,[1,4] Maikel P. Peppelenbosch,[1] Jiaye Liu,[1] and Qiuwei Pan[1]

[1]Department of Gastroenterology and Hepatology, Erasmus MC-University Medical Center, Rotterdam, The Netherlands, [2]Department of Hepatobiliary Surgery, Daping Hospital (Army Medical Center), Third Military Medical University (Army Medical University), Chongqing, China, [3]Biomedical Research Center, Northwest Minzu University, Lanzhou, People's Republic of China, [4]Department of Infectious Diseases, Molecular Virology, University Hospital Heidelberg, Heidelberg, Germany

J Chin Med Assoc
ORIGINAL ARTICLE

Hepatitis D virus dual infection increased the risk of hepatocellular carcinoma compared with hepatitis B virus mono infection: A meta-analysis

Tien-En Chang[a,b,c], Chien-Wei Su[a,b,d,*], Yi-Shin Huang[a,b], Yi-Hsiang Huang[a,f], Ming-Chih Hou[a,b], Jaw-Ching Wu[e,f,g,*]

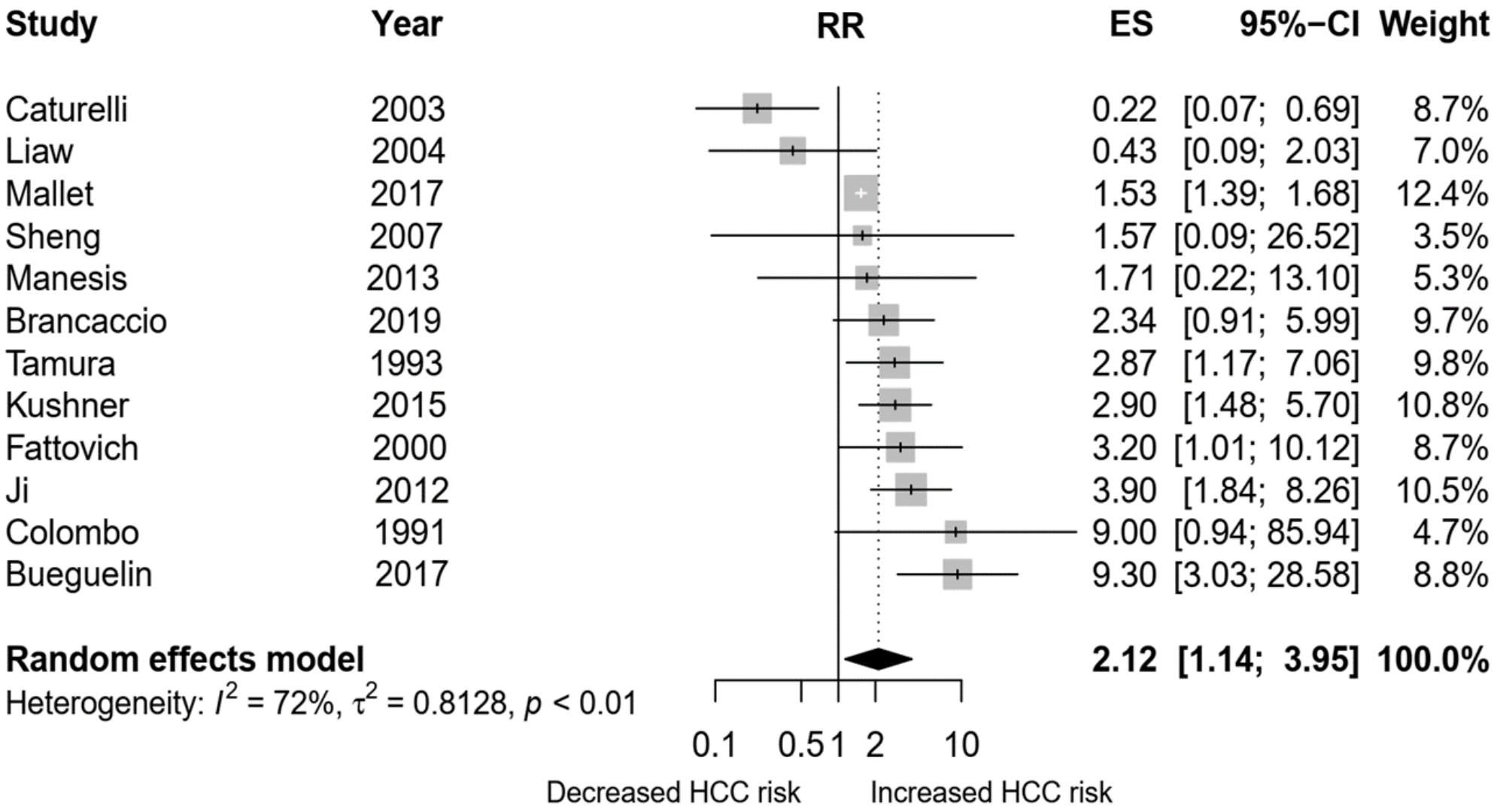
ORIGINAL ARTICLE

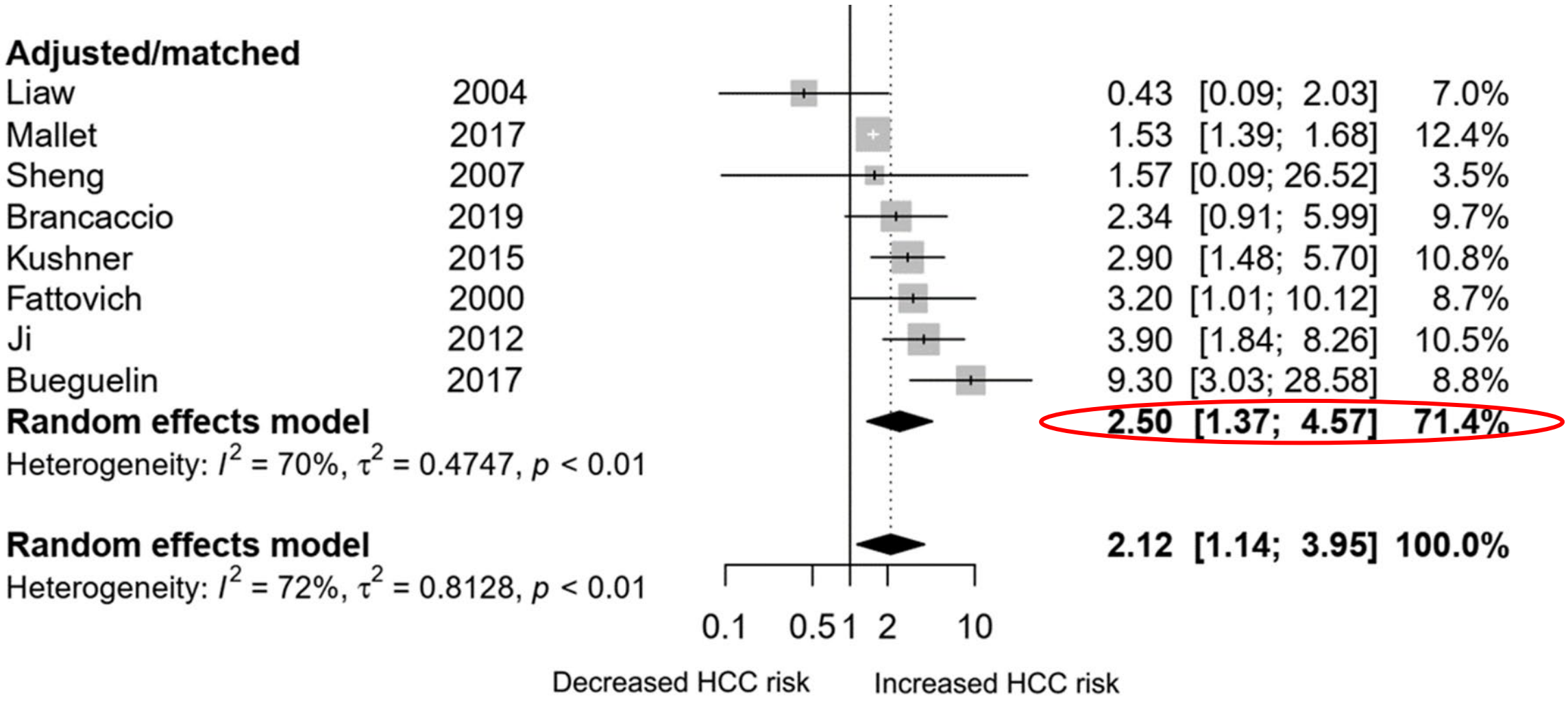
JOURNAL OF VIRAL HEPATITIS JVH WILEY

Risk of hepatocellular carcinoma in hepatitis B and D virus co-infected patients: A systematic review and meta-analysis of longitudinal studies

Habiba Kamal[1,2] | Romina Fornes[3] | Johanna Simin[3] | Per Stål[2,4] | Ann-Sofi Duberg[5] | Nele Brusselaers[3] | Soo Aleman[1,2]

Parameter	HBV/HDV mono-infection N=6,099	HBV mono-infection N=57,620
Age at baseline	40.4	45.9
Male proportions	54.7% to 97.0%	58.4% to 96.4%
Liver cirrhosis	57.2%	15.5%


Study
Year
RR
ES
95%−CI
Weight
Caturelli 2003 0.22 [0.07; 0.69] 8.7%
Liaw 2004 0.43 [0.09; 2.03] 7.0%
Mallet 2017 1.53 [1.39; 1.68] 12.4%
Sheng 2007 1.57 [0.09; 26.52] 3.5%
Manesis 2013 1.71 [0.22; 13.10] 5.3%
Brancaccio 2019 2.34 [0.91; 5.99] 9.7%
Tamura 1993 2.87 [1.17; 7.06] 9.8%
Kushner 2015 2.90 [1.48; 5.70] 10.8%
Fattovich 2000 3.20 [1.01; 10.12] 8.7%
Ji 2012 3.90 [1.84; 8.26] 10.5%
Colombo 1991 9.00 [0.94; 85.94] 4.7%
Bueguelin 2017 9.30 [3.03; 28.58] 8.8%
Random effects model 2.12 [1.14; 3.95] 100.0%
Heterogeneity: I^2 = 72%, τ^2 = 0.8128, p < 0.01
0.1 0.5 1 2 10
Decreased HCC risk
Increased HCC risk


Adjusted/matched
Liaw 2004 0.43 [0.09; 2.03] 7.0%
Mallet 2017 1.53 [1.39; 1.68] 12.4%
Sheng 2007 1.57 [0.09; 26.52] 3.5%
Brancaccio 2019 2.34 [0.91; 5.99] 9.7%
Kushner 2015 2.90 [1.48; 5.70] 10.8%
Fattovich 2000 3.20 [1.01; 10.12] 8.7%
Ji 2012 3.90 [1.84; 8.26] 10.5%
Bueguelin 2017 9.30 [3.03; 28.58] 8.8%
Random effects model 2.50 [1.37; 4.57] 71.4%
Heterogeneity: I^2 = 70%, τ^2 = 0.4747, p < 0.01
Random effects model 2.12 [1.14; 3.95] 100.0%
Heterogeneity: I^2 = 72%, τ^2 = 0.8128, p < 0.01
0.1 0.5 1 2 10
Decreased HCC risk
Increased HCC risk

Among NUC experienced patients, still HCC risk is increased

WILEY AP&T Alimentary Pharmacology & Therapeutics

Clinical outcomes in patients with hepatitis D, cirrhosis and persistent hepatitis B virus replication, and receiving long-term tenofovir or entecavir

Giuseppina Brancaccio[1,2] | Massimo Fasano[3] | Adriano Grossi[1] | Teresa Antonia Santantonio[3] | Giovanni B. Gaeta[1]

scientific reports

Check for updates

OPEN

Role of hepatitis D virus infection in development of hepatocellular carcinoma among chronic hepatitis B patients treated with nucleotide/nucleoside analogues

Tyng-Yuan Jang[1,2,3], Yu-Ju Wei[1,4], Ta-Wei Liu[1,4], Ming-Lun Yeh[1,5], Shu-Fen Liu[1], Cheng-Ting Hsu[1], Po-Yao Hsu[1], Yi-Hung Lin[1], Po-Cheng Liang[1], Meng-Hsuan Hsieh[1,5,6,7,8], Yu-Min Ko[1], Yi-Shan Tsai[1], Kuan-Yu Chen[1], Ching-Chih Lin[1], Pei-Chien Tsai[1], Shu-Chi Wang[8], Ching-I. Huang[1,5], Zu-Yau Lin[1,5], Shinn-Cherng Chen[1,5], Wan-Long Chuang[1,5], Jee-Fu Huang[1,4,5], Chia-Yen Dai[1,5], Chung-Feng Huang[1,5,8,9] & Ming-Lung Yu[1,5,9]

Original Article

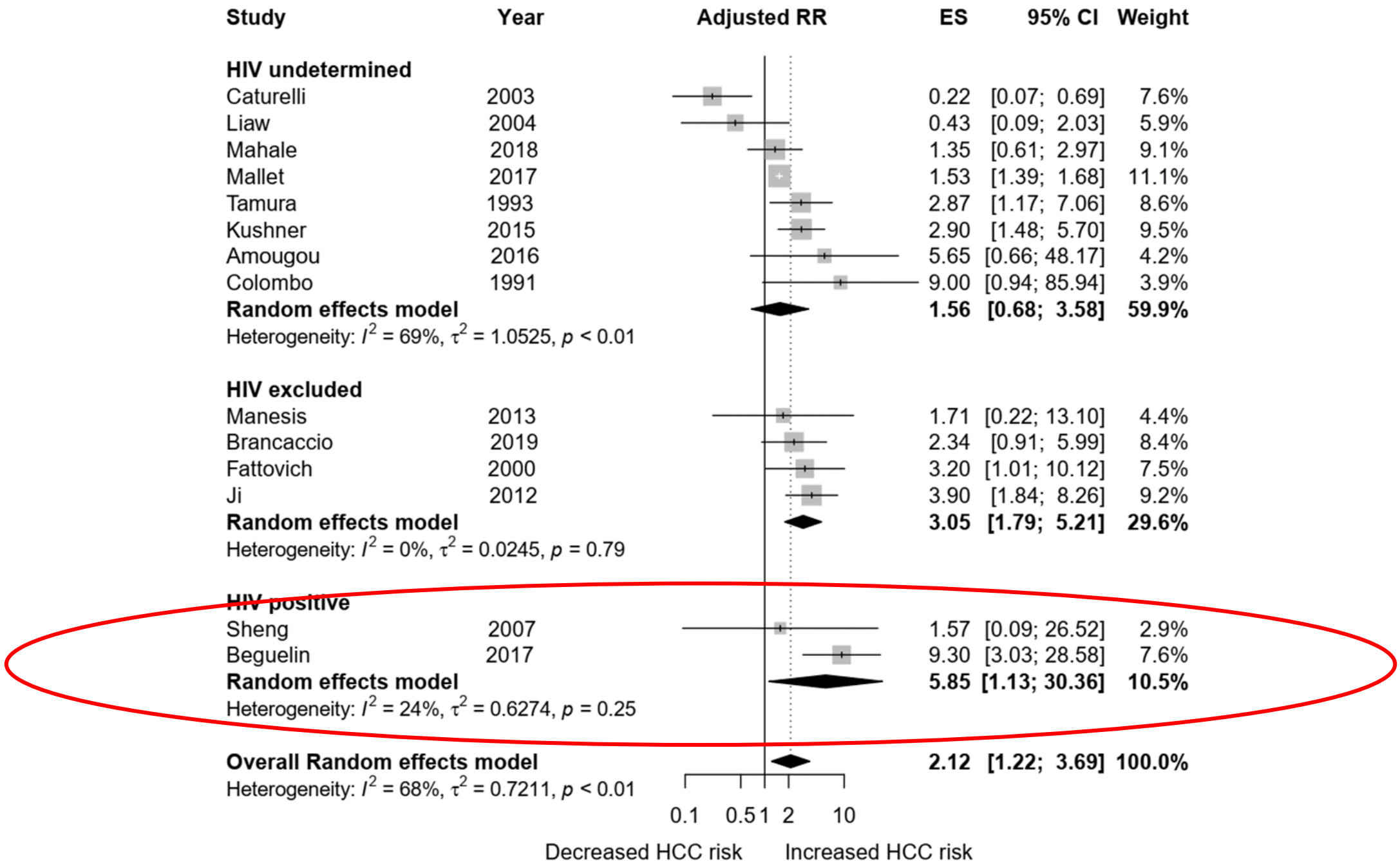
Hepatocellular Carcinoma in Hepatitis D: Does it Differ from Hepatitis B Monoinfection?

Zaigham Abbas, Mustafa Qureshi, Saeed Hamid, Wasim Jafri

- Comparison between 92 patients with HBV –related HCC and 92 patients with HBV/HDV-related HCC.
- HDV-related HCC tended to have decreased liver size, patients had lower platelets and larger varices on endoscopy.
- Multifocal tumours, advanced HCC stages and elevated alpha-fetoprotein level were more common in HBV group.

People living with triple infection HIV/HBV/HDV infection

- A particular higher risk in PLHIV demonstrated in prospective register-based studies and pooled analyses as well.
- ~10% of PLHIV are coinfected with HBV.
- Reflex testing recommendation is still missing.


Study
Year
Adjusted RR
ES
95% CI
Weight
HIV undetermined
Caturelli 2003 0.22 [0.07; 0.69] 7.6%
Liaw 2004 0.43 [0.09; 2.03] 5.9%
Mahale 2018 1.35 [0.61; 2.97] 9.1%
Mallet 2017 1.53 [1.39; 1.68] 11.1%
Tamura 1993 2.87 [1.17; 7.06] 8.6%
Kushner 2015 2.90 [1.48; 5.70] 9.5%
Amougou 2016 5.65 [0.66; 48.17] 4.2%
Colombo 1991 9.00 [0.94; 85.94] 3.9%
Random effects model 1.56 [0.68; 3.58] 59.9%
Heterogeneity: I^2 = 69%, τ^2 = 1.0525, p < 0.01
HIV excluded
Manesis 2013 1.71 [0.22; 13.10] 4.4%
Brancaccio 2019 2.34 [0.91; 5.99] 8.4%
Fattovich 2000 3.20 [1.01; 10.12] 7.5%
Ji 2012 3.90 [1.84; 8.26] 9.2%
Random effects model 3.05 [1.79; 5.21] 29.6%
Heterogeneity: I^2 = 0%, τ^2 = 0.0245, p = 0.79
HIV positive
Sheng 2007 1.57 [0.09; 26.52] 2.9%
Beguelin 2017 9.30 [3.03; 28.58] 7.6%
Random effects model 5.85 [1.13; 30.36] 10.5%
Heterogeneity: I^2 = 24%, τ^2 = 0.6274, p = 0.25
Overall Random effects model 2.12 [1.22; 3.69] 100.0%
Heterogeneity: I^2 = 68%, τ^2 = 0.7211, p < 0.01
0.1
0.5
1
2
10
Decreased HCC risk
Increased HCC risk

Limitations of the pooled analyses

- Testing for HDV RNA is not uniform among the studies.
- A main limitation (missing information for patients on treatment).
- Significant heterogeneity between the studies.
- Genotypes influence could not be assessed

Other confounders…

- Historical among patients who use intravenous drugs, polyblood transfusion…
- Endemic regions have other comorbidities (HCV, parasitic liver diseases, exposure to other environmental toxins like aflatoxin B1…)
- Scarcity on the prevalence and influence of metabolic associated liver diseases

HCC surveillance in HDV

TABLE 1. PATIENTS AT THE HIGHEST RISK FOR HCC

Population Group	Threshold Incidence for Efficacy of Surveillance (>0.25 LYG; % per year)	Incidence of HCC
Surveillance benefit		
Asian male hepatitis B carriers over age 40	0.2	0.4%-0.6% per year
Asian female hepatitis B carriers over age 50	0.2	0.3%-0.6% per year
Hepatitis B carrier with family history of HCC	0.2	Incidence higher than without family history
African and/or North American blacks with hepatitis B	0.2	HCC occurs at a younger age
Hepatitis B carriers with cirrhosis	0.2-1.5	3%-8% per year
Hepatitis C cirrhosis	1.5	3%-5% per year
Stage 4 PBC	1.5	3%-5% per year
Genetic hemochromatosis and cirrhosis	1.5	Unknown, but probably >1.5% per year
Alpha-1 antitrypsin deficiency and cirrhosis	1.5	Unknown, but probably >1.5% per year
Other cirrhosis	1.5	Unknown
Surveillance benefit uncertain		
Hepatitis B carriers younger than 40 (males) or 50 (females)	0.2	<0.2% per year
Hepatitis C and stage 3 fibrosis	1.5	<1.5% per year
NAFLD without cirrhosis	1.5	<1.5% per year

Abbreviation: LYG, life-years gained.

Table 3. Recommendations for HCC surveillance: Categories of adult patients in whom surveillance is recommended.

- Cirrhotic patients, Child-Pugh stage A and B (**evidence low; recommendation strong**)
- Cirrhotic patients, Child-Pugh stage C awaiting liver transplantation (**evidence low; recommendation strong**)
- Non-cirrhotic HBV patients at intermediate or high risk of HCC* (according to PAGE-B† classes for Caucasian subjects, respectively 10–17 and ≥18 score points) (**evidence low; recommendation weak**)
- Non-cirrhotic F3 patients, regardless of aetiology may be considered for surveillance based on an individual risk assessment (**evidence low; recommendation weak**)

*Patients at low HCC risk left untreated for HBV and without regular six months surveillance must be reassessed at least yearly to verify progression of HCC risk.
†PAGE-B (Platelet, Age, Gender, hepatitis B) score is based on decade of age (16–29 = 0, 30–39 = 2, 40–49 = 4, 50–59 = 6, 60–69 = 8, ≥70 = 10), gender (M = 6, F = 0) and platelet count (≥200,000/μl = 0, 100,000–199,999/μl = 1, <100,000/μl = 2): a total sum of ≤9 is considered at low risk of HCC (almost 0% HCC at five years) a score of 10–17 at intermediate risk (3% incidence HCC at five years) and ≥18 is at high risk (17% HCC at five years).[114]

Treatment of HDV

- Evidence from 30 years of off label use of IFN therapy in CHD.
- IFN therapy is a suboptimal therapy with VR 20-30% in eligible patients who can tolerate 48 weeks of SC peg IFN.
- Multiple studies pointed the benefit of IFN in decreasing liver-related events and possibly HCC, especially with prolongation of therapy
- NUC therapy role in HDV.

Towards…

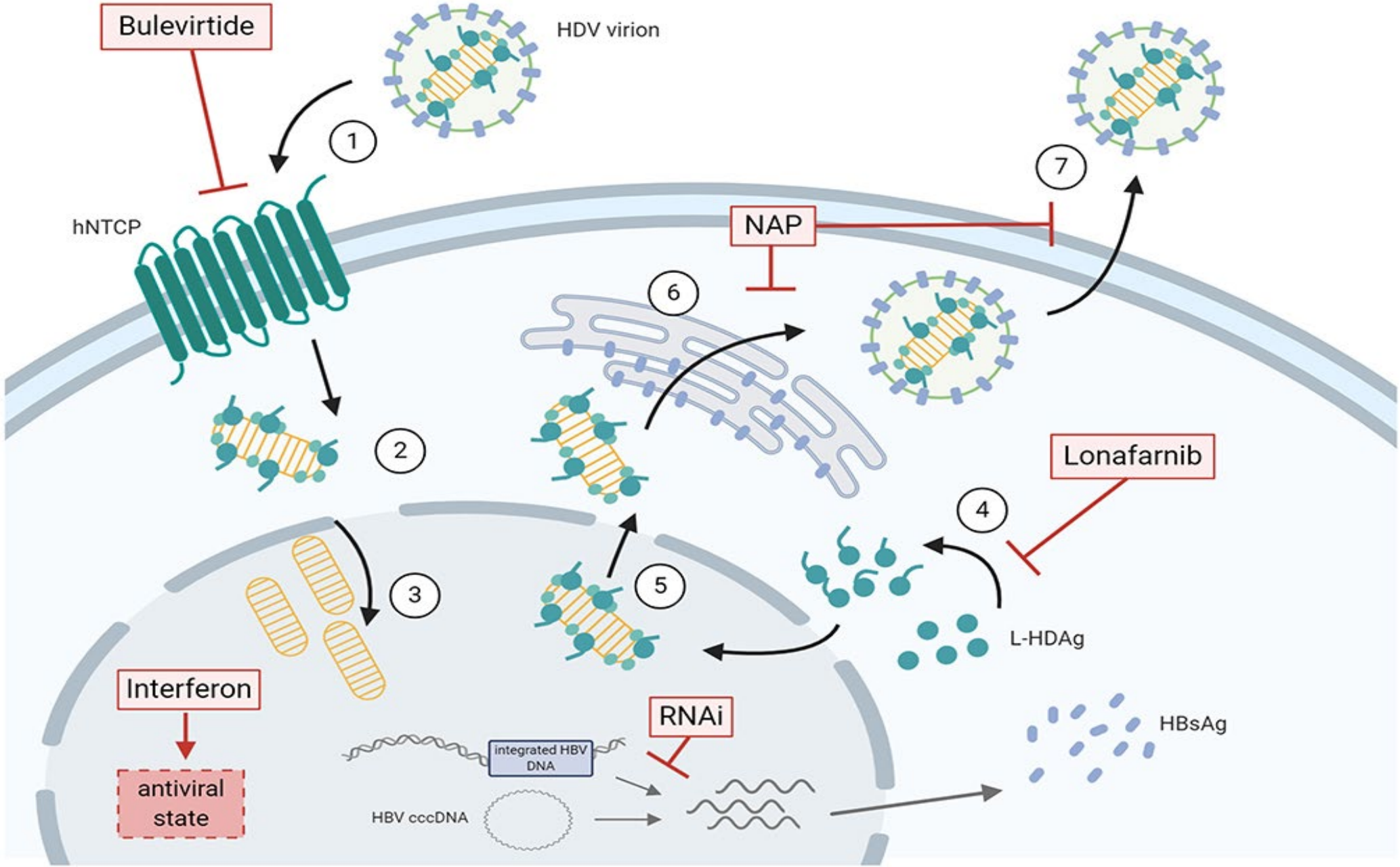
- Reflex testing of all chronic HBV carriers.
- More prospective studies conducted in regions of high endemicity
- New therapies

My thanks

- My PhD supervisors:

  Soo Aleman, Ann-Sofi Duberg, Per Stål and Heiner Wedemeyer.

- My co-author Romina Fornes from Nele Brussealers research group.
- KI librarians for conducting the search.
- Patients living with HDV, their families and care givers.


Bulevirtide
HDV virion
1
hNTCP
7
NAP
6
2
Lonafarnib
4
3
5
L-HDAg
Interferon
RNAi
HBsAg
integrated HBV DNA
antiviral state
HBV cccDNA