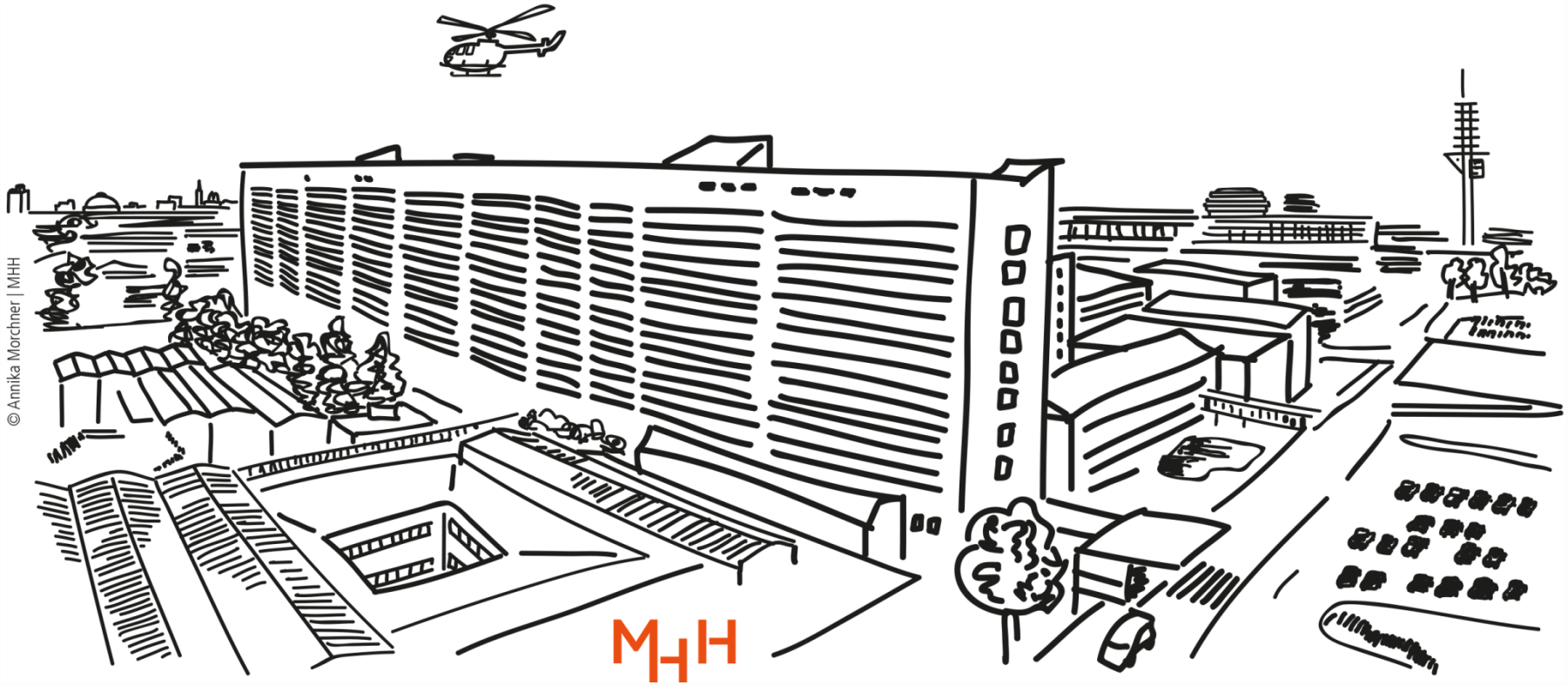
Whats new on HBsAg and other markers for HBV infection?



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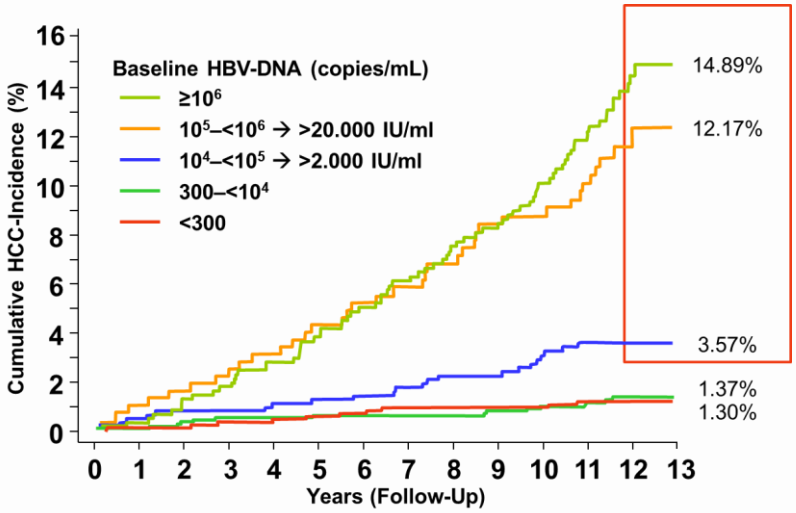
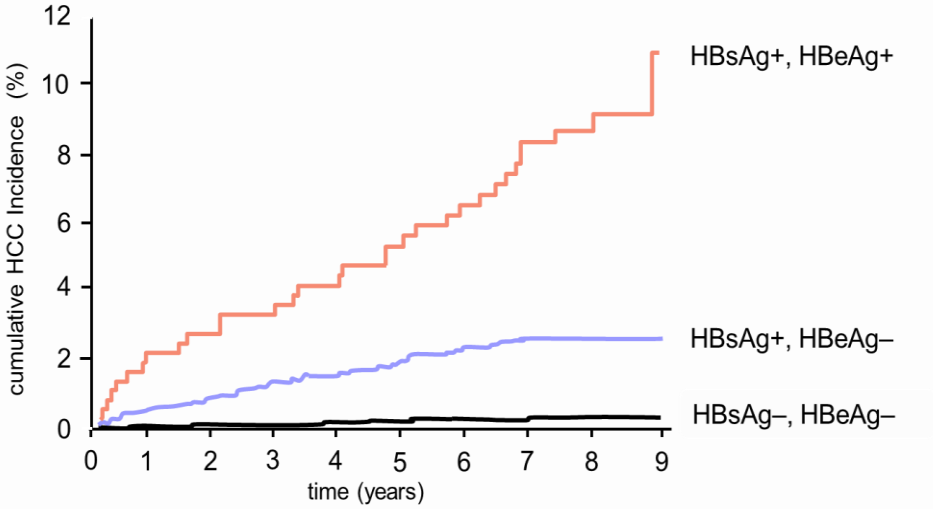
Why diagnostic markers are important

- They are the basis for clinical decision makings
  - treatment or no treatment?
  - progress or no progress?
  - HCC or no HCC?
  - cured or not cured?

Viral markers associated with „hard“ outcomes





HBV DNA

HBsAg, HBeAg

Yang et al. NEJM 2002
REVEAL study: Chen et al., JAMA 2006

HBeAg positive patients

HBsAg >100,000 U/ml indicative for "**immune tolerance**" (33)

HBsAg > 25,000 U/ml has >90% PPV for **liver fibrosis <F1** (32).

HBsAg levels <3.85log IU/ml are associated with **moderate to severe fibrosis** (36) (100%-sensitivity, 86%-specificity and 100%-negative predictive value (NPV) in genotype B and C patients (higher in GT A/D))

The challenge is to determine fibrosis or hepatic necroinflammation!

HBeAg negative patients

HBsAg < 1,000 IU/ml and HBV DNA <2,000 IU/ml has high PPV (83%-87.9%) in for **inactive carrier phase and reduced risk for HCC** (42, 44).

Low HBsAg titer (<200 IU/ml, <100 IU/ml) are also **predictive for subsequent HBsAg loss** (47–49).

Challenge: 10%–20% individuals may experience **reactivation** and 4-20% may revert back to **HBeAg positive hepatitis**

On treatment marker – PEG-IFN

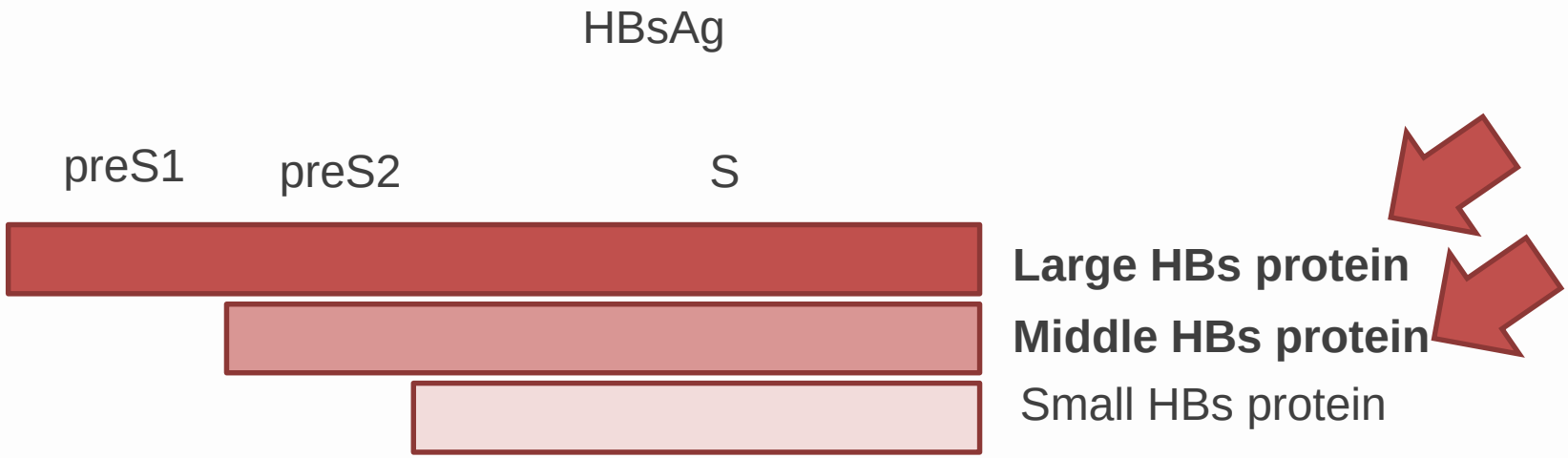
HBeAg pos.	HBsAg <1,500 IU/ml at week 12 corresponds to 57% PPV for anti-HBe seroconversion and 17.6% HBsAg clearance. No decline of HBsAg until week 12 showed a **NPV of 97%-100**% for Genotype A and D). HBsAg at week 12 >20,000 IU/mL showed a **NPV of 92%-98%** for Genotype B and C). HBsAg > 20.000 IU/ml at week 24 associated with **100% NPV** for anti-HBe seroconversion.
HBeAg neg.	No HBsAg decline (any decline) and <2 log decline of HBV DNA showed a **NPV of 100%** for nonresponse in genotype D patients.

On treatment marker- NA

- In patients treated with tenofovir, a reduction in HBsAg level of at least 1 log by week 12 or 24 were **predictive for HBsAg loss** with a positive predictive value of up to 45% and a NPV of up to 97%.
- HBsAg levels <100 IU/ml after 2 years of NA treatment may help to predict **stable anti-HBe serconversion** and stable virological and biochemical response in HBeAg positive patients
- Consolidation therapy of > 3 years and suppressed HBV DNA > 2 years increase the chance of stable off-therapy response in HBeAg negative patients who discontinue treatment. Low level of HBsAg (i.e. <100 IU/ml) are associated with **off-treatment response.**

Marcellin P et al.J Hepatol 2014;61:1228–1237.

How can HBsAg testing be improved?



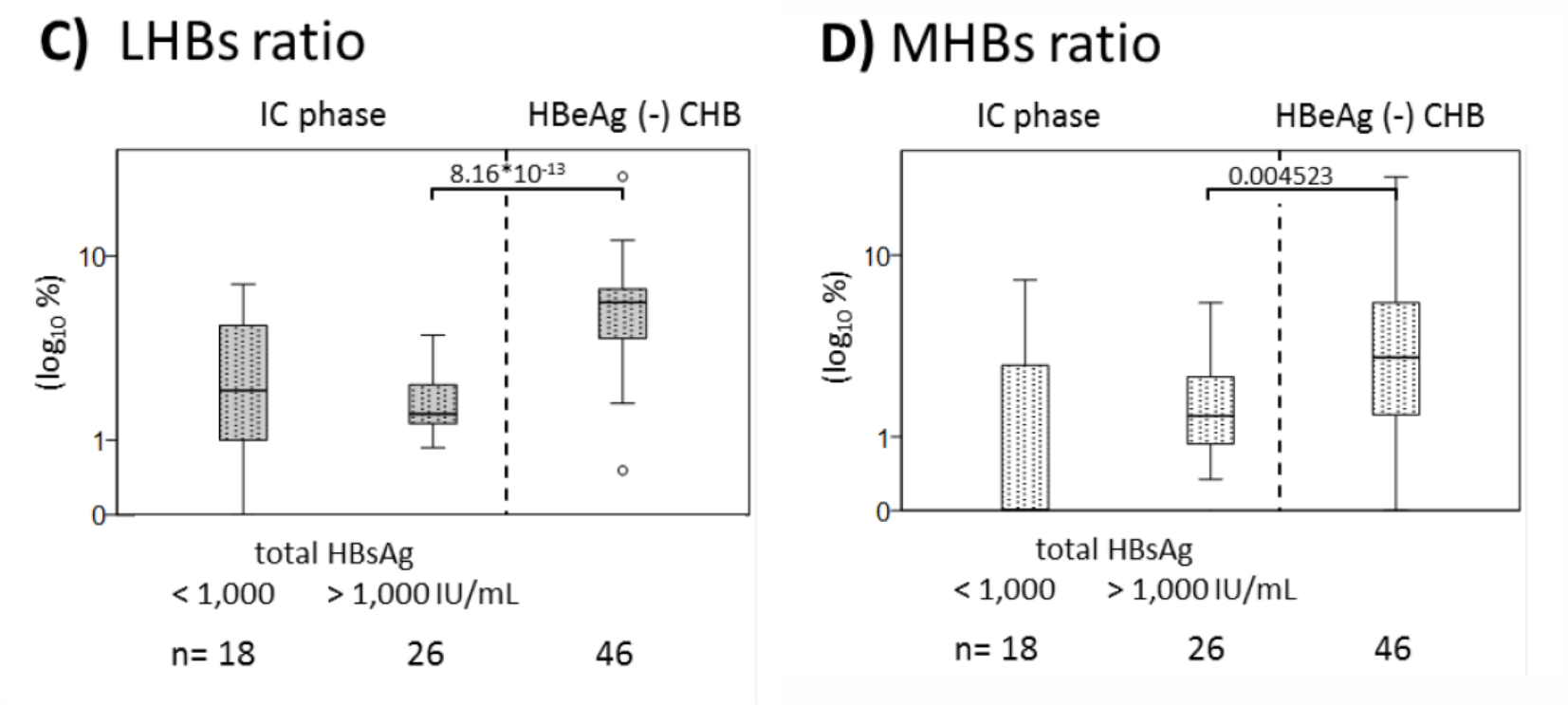
The ratio of LHBs, MHBs and SHBs is distinct for specific infection phases

	(a) ICs	(c) HBeAg-negative CHB	(a) vs (c)
LHBs (log_{10} ng/mL)*	1.9±0.5 (–1.9–2.92; 1 nd)	2.5±0.6 (0.7–3.6)	3.2×10^{-7}
MHBs (log_{10} ng/mL)*	1.8±0.6 (0.8–2.9; 10 nd)	2.1±0.8 (0.1–3.5; 1nd)	0.0003
SHBs (log_{10} ng/mL)*	3.1±1.1 (0.5–4.5)	3.6±0.5 (2.1–4.8)	0.0777
total HBsAg (log_{10} ng/mL)*	3.1±1.1 (0.5–4.5)	3.7±0.6 (2.1–4.8)	0.4809
LHBs (%)*	2.3±1.6 (0.0–7.5)	6.0±3.3 (0.5–22.0)	3.1×10^{-12}
MHBs (%)*	1.8±1.9 (0.0–7.7)	4.4±4.3 (0.0–22.0)	8.3×10^{-4}
SHBs (%)*	95.9–2.6 (89.6–100.0)	89.6±5.8 (65.7–99.0)	4.1×10^{-11}

*Mean±SD (range).

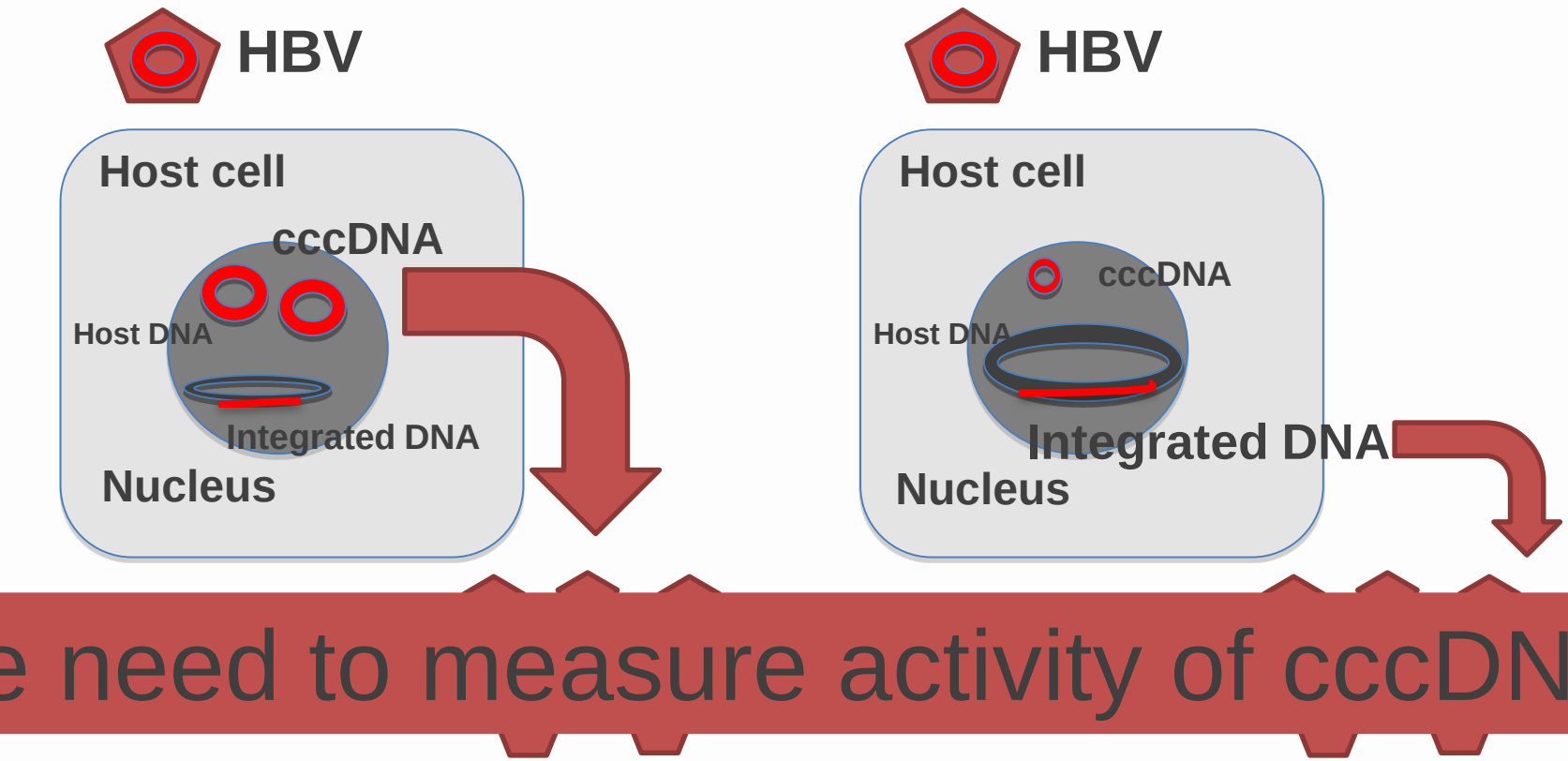
Pfefferkorn M, et al. Gut 2017;**0**:1–9. doi:10.1136/gutjnl-2017-313811

LHBs may be a better marker than HBsAg to verify HBeAg negative infection (inactive carriers)



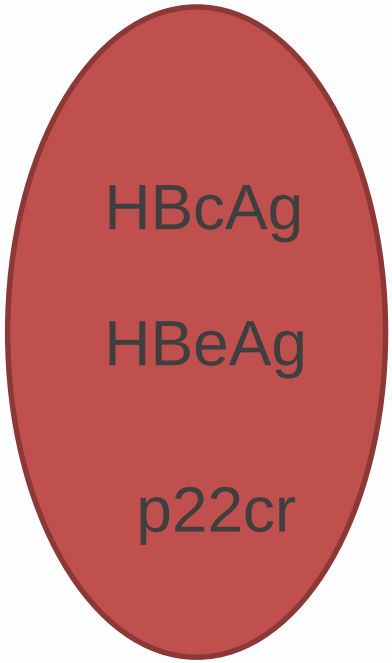
Pfefferkorn M, et al. Gut 2017;**0**:1–9. doi:10.1136/gutjnl-2017-313811

Major challenge – the HBV life cycle



Woodell et al. Sci Transl Med 2017, 9:eaan0241.

Hepatitis B core-related antigen (HBcrAg)



HBcrAg

= composite marker, reflecting the activity of cccDNA

HBcrAg correlates well with HBV DNA and intrahepatic cccDNA

No. of subjects	Correlation coefficient	*P* value	References
190	.79 (genotype B)[a] .87 (genotype C)[a]	<.001 <.001	19
82	Overall: .807	<.001	20
	HBeAg-positive: .847	<.001	
	HBeAg-negative: .632	<.001	
93	.820[a]	<.001	21
138	Overall: .69	<.0001	22
	HBeAg-positive: .66	<.0001	
	HBeAg-negative: .59	<.0001	

HBV DNA

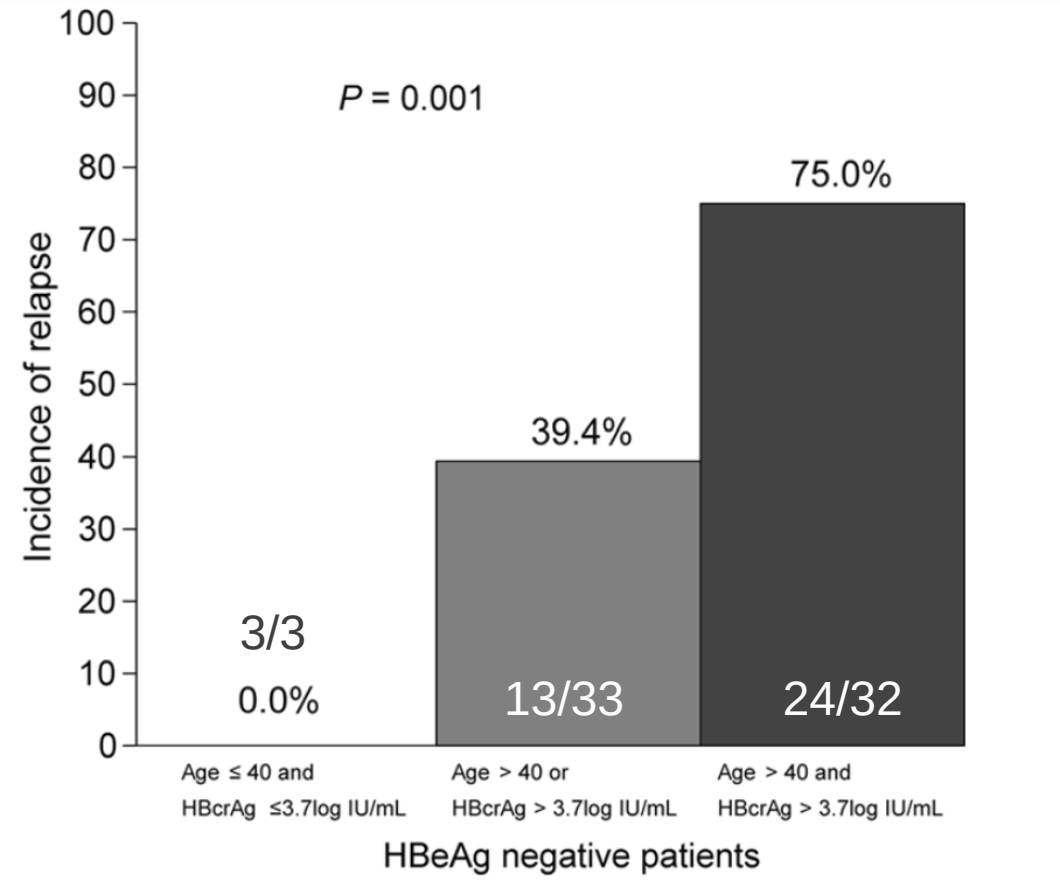
No. of subjects	Correlation coefficient	*P* value	References
93	.664	<.001	21
138	.70	<.0001	22
31	.482	<.006	24

Intrahepatic cccDNA

HBcrAg detectable in 78% of patients with undetectable HBV DNA due to antiviral therapy!

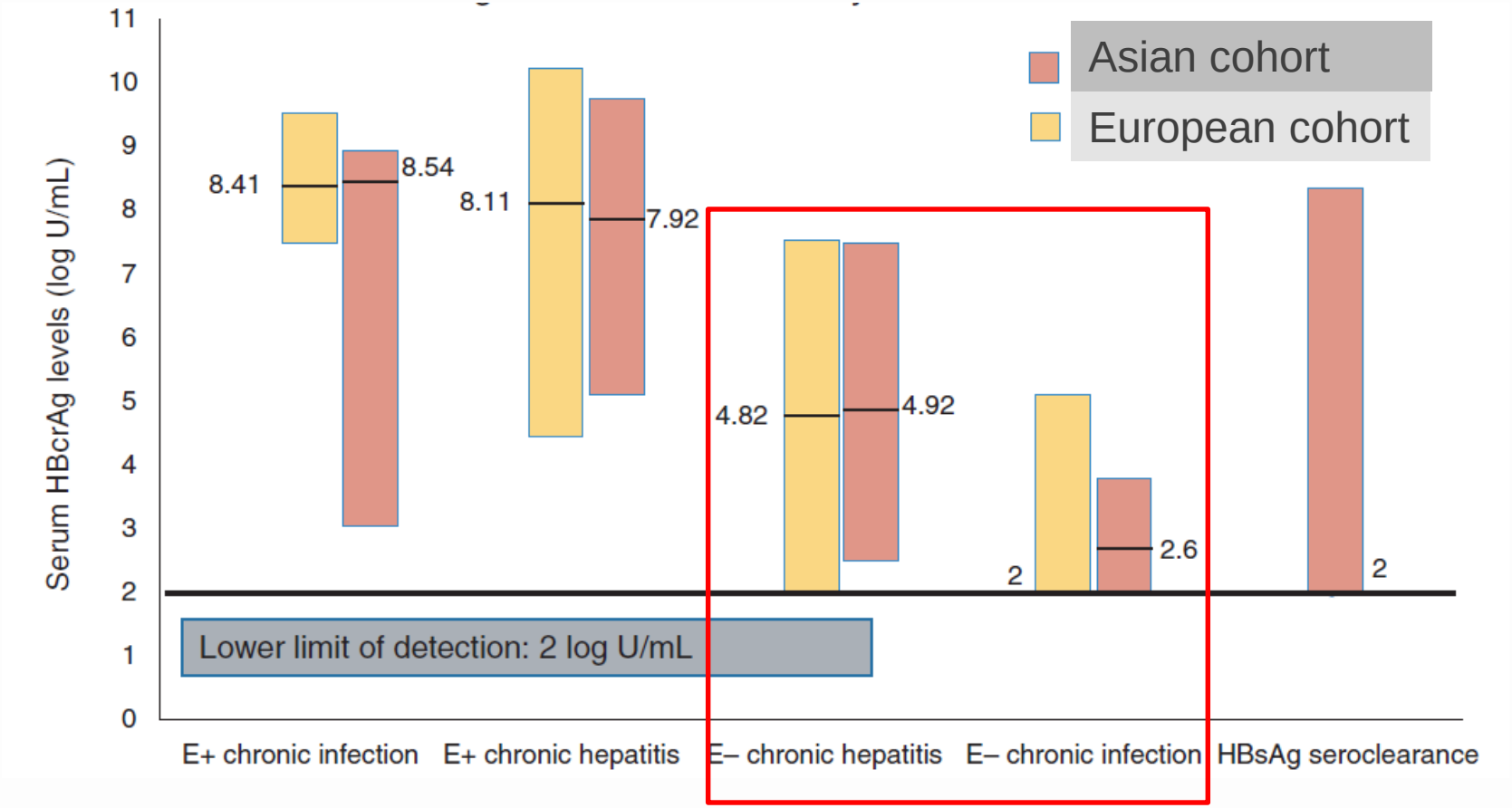
Mak et al. Aliment Pharmacol Ther. 2018;47:43–54
Wong et al. J Clin Microbiol. 2007;45:3942-3947.

EOT- HBcrAg as a marker to predict relapse after stop of NA treatment



Jung et al. J Gastroenterol. 2016;51:830-839.

HBcrAg as a marker in HBeAg negative infection



Maasoumy et al. Clin Microbiol Infect. 2015;21:606 e1-606e10.
Seto et al. Clin Microbiol Infect. 2014;20:1173-1180.
Mak et al. Aliment Pharmacol Ther. 2018;47:43–5
Riveiro-Barciela et al Clin Microbiol Infect 2017. 4

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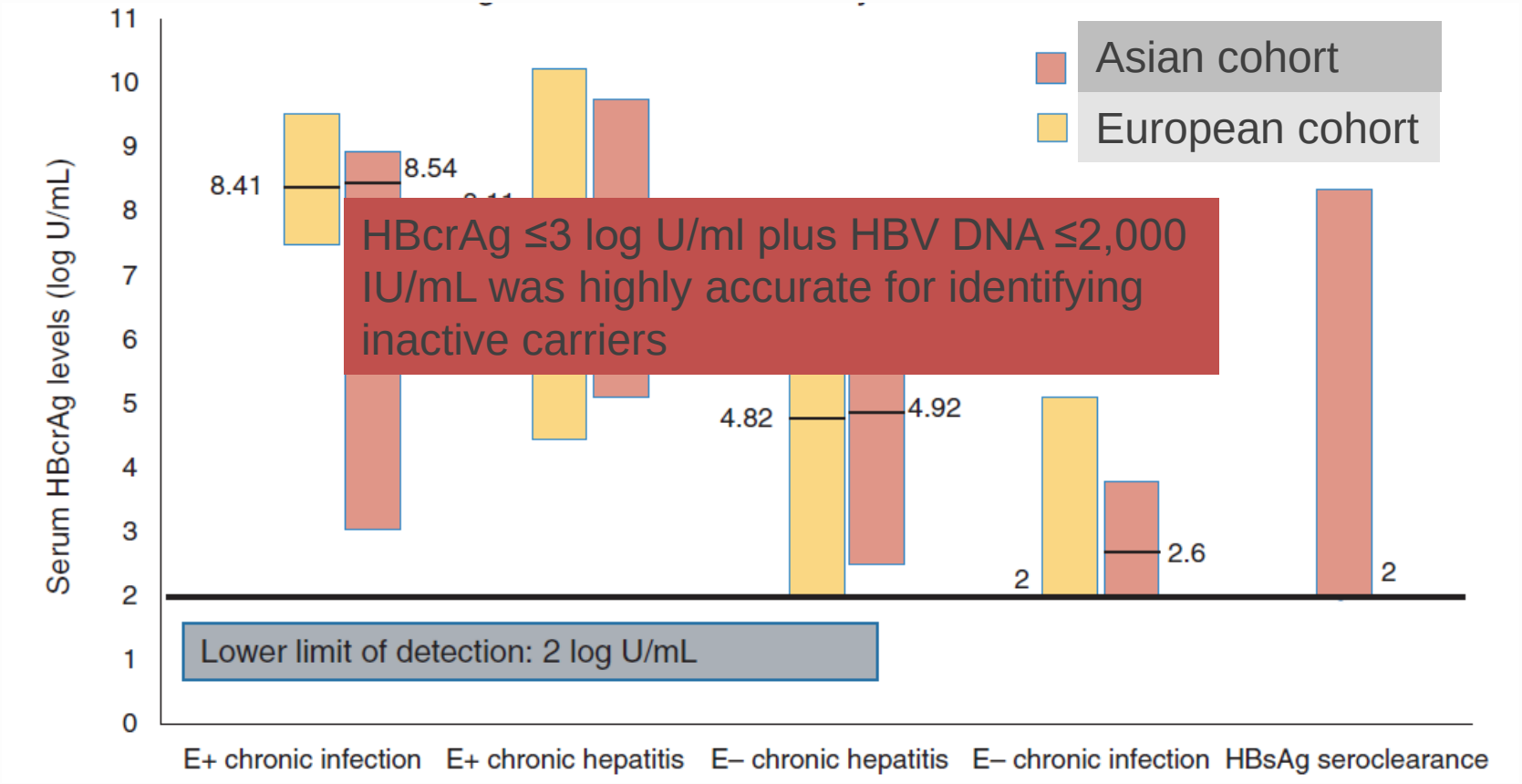

Maasoumy et al. Clin Microbiol Infect. 2015;21:606 e1-606e10.
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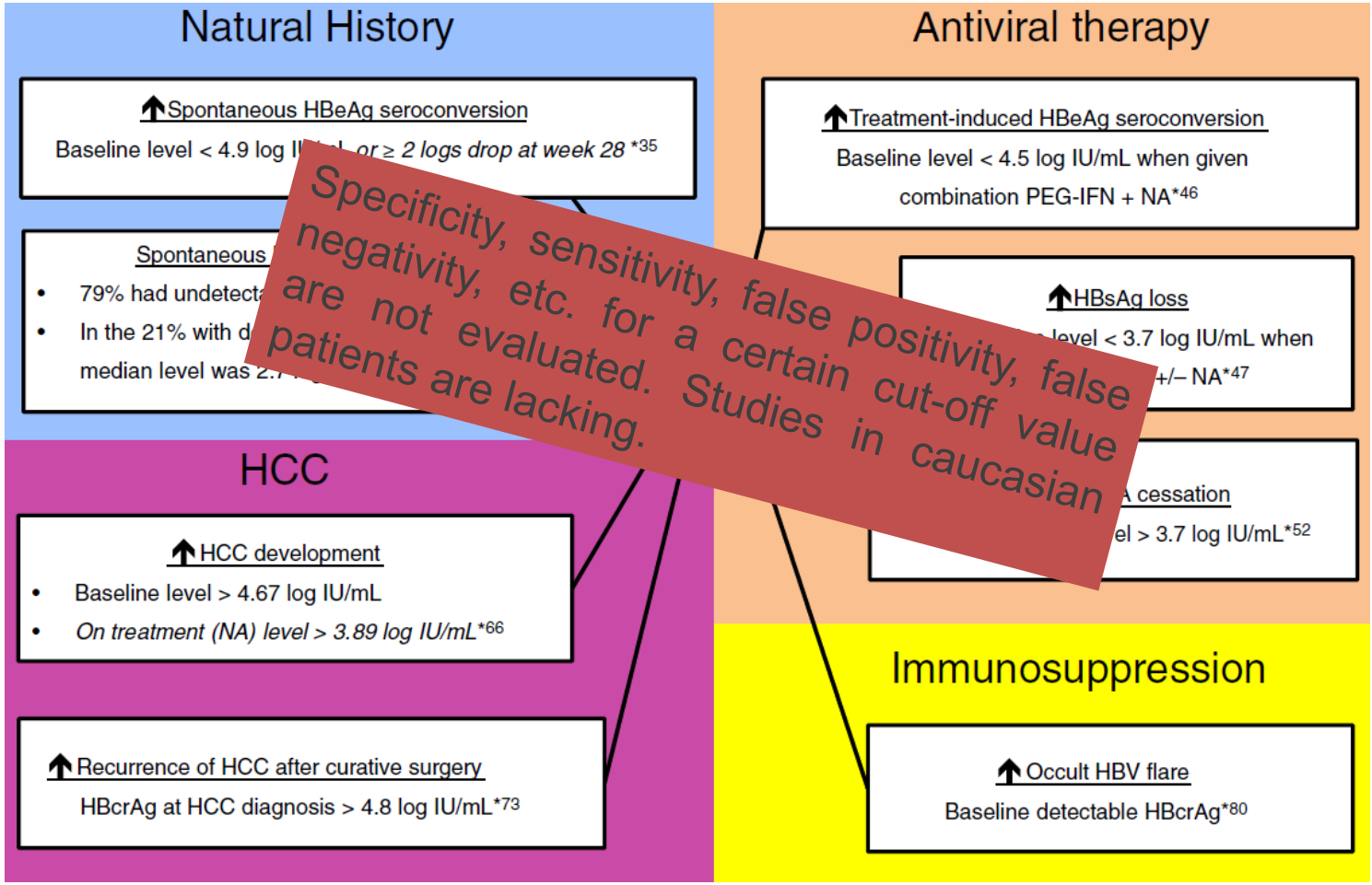
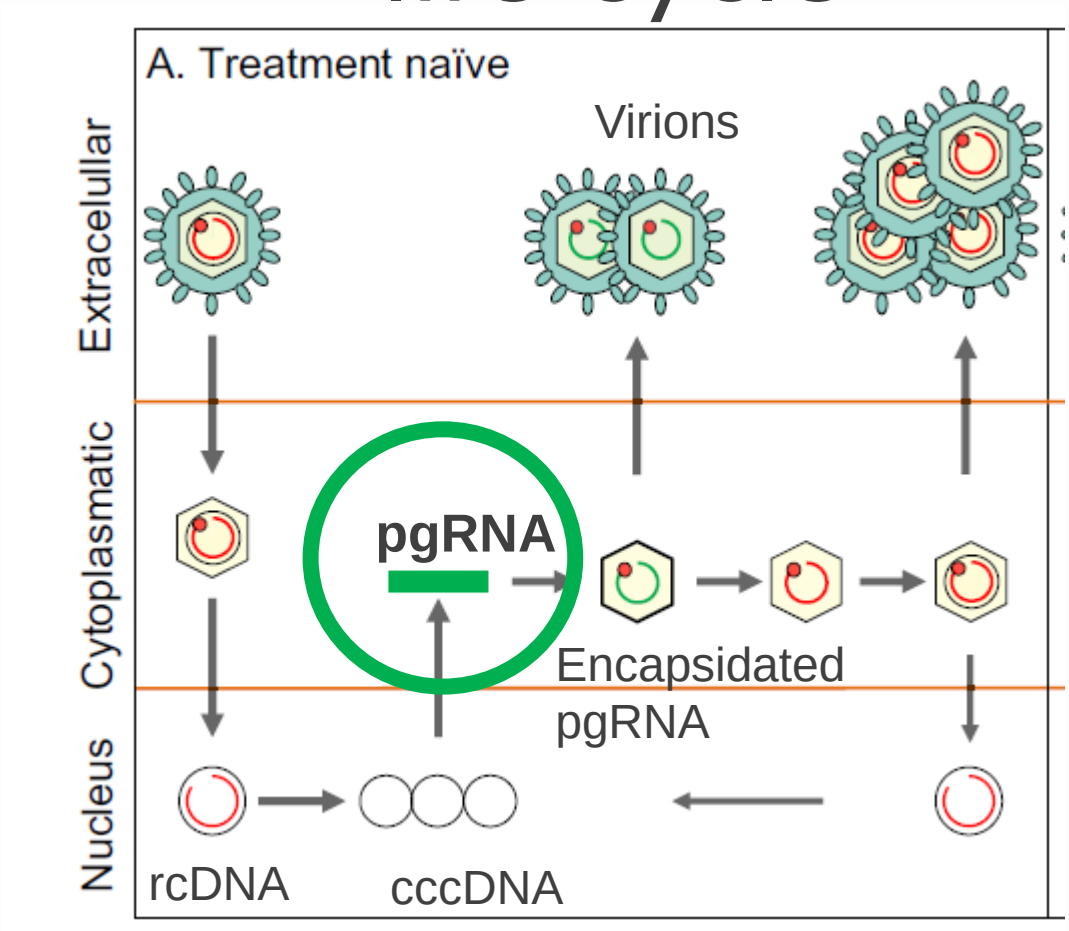
Riveiro-Barciela et al Clin Microbiol Infect 2017. 4

Several applications of HBcrAg



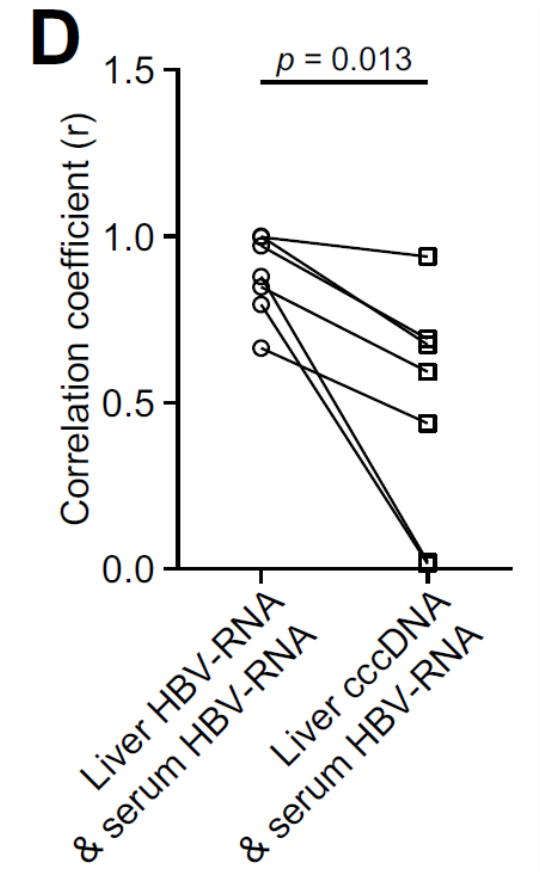
Mak et al. Aliment Pharmacol Ther. 2018;47:43–54

HBV RNA – central for the HBV life cycle



Wang et al. Journal of Hepatology 2016 vol. 65 j 700–710

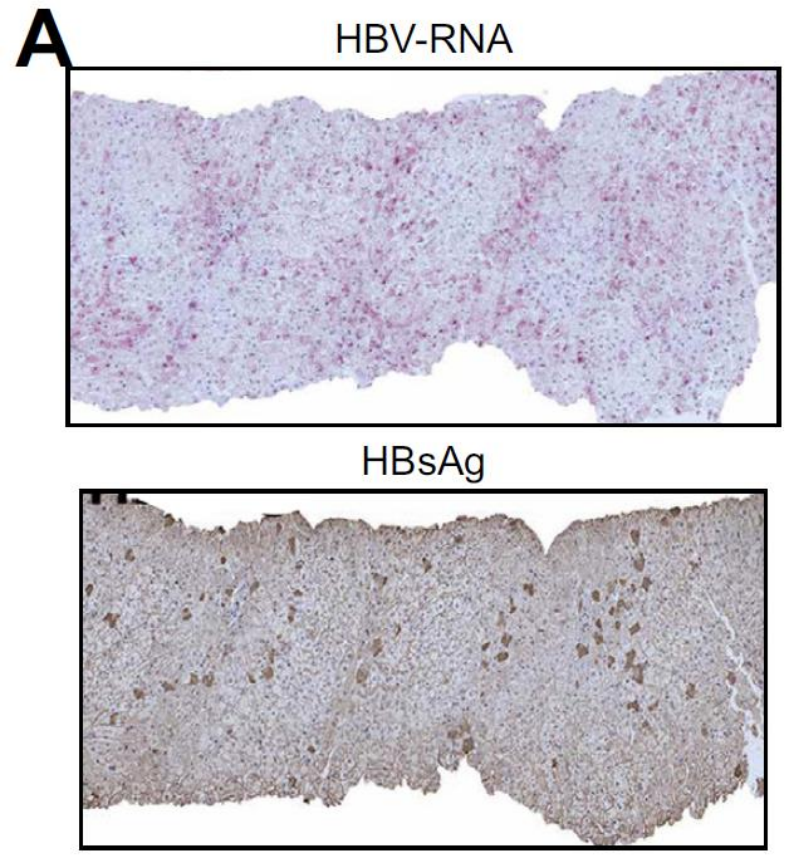
Serum HBV-RNA resembles intrahepatic viral RNA but not cccDNA



Quasispecies of serum HBV-RNA and intrahepatic HBV-RNA and cccDNA.

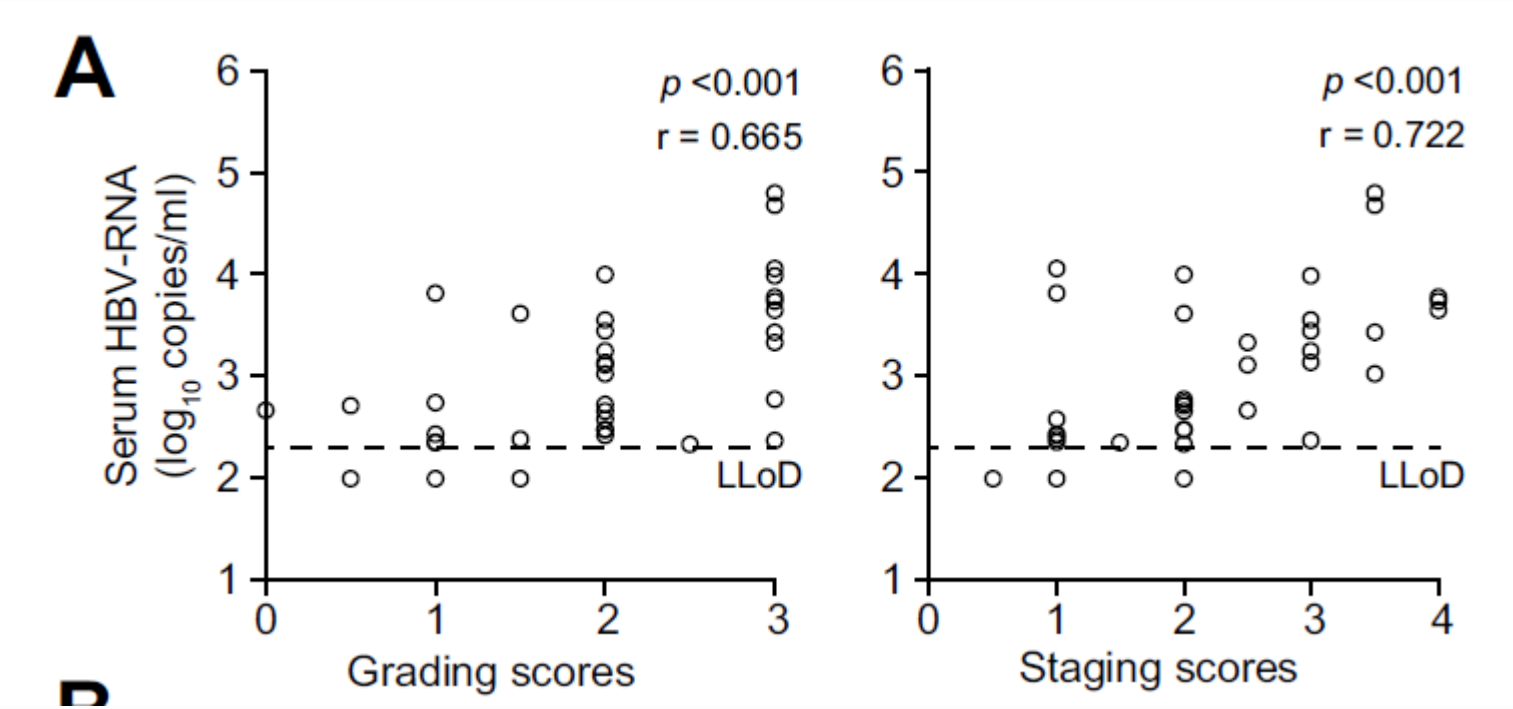
Wang et al. Journal of Hepatology 2018 vol. 68 j 16–24

Production of viral RNA is ongoing despite suppressed HBV DNA



Wang et al. Journal of Hepatology 2018 vol. 68 j 16–24

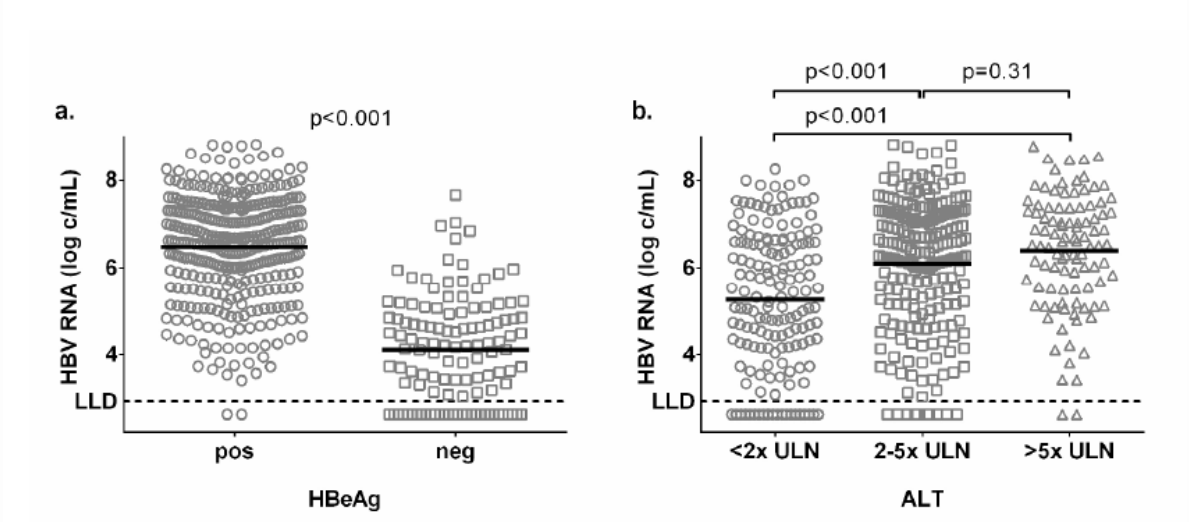
HBV-RNA correlates with necroinflammation and fibrosis

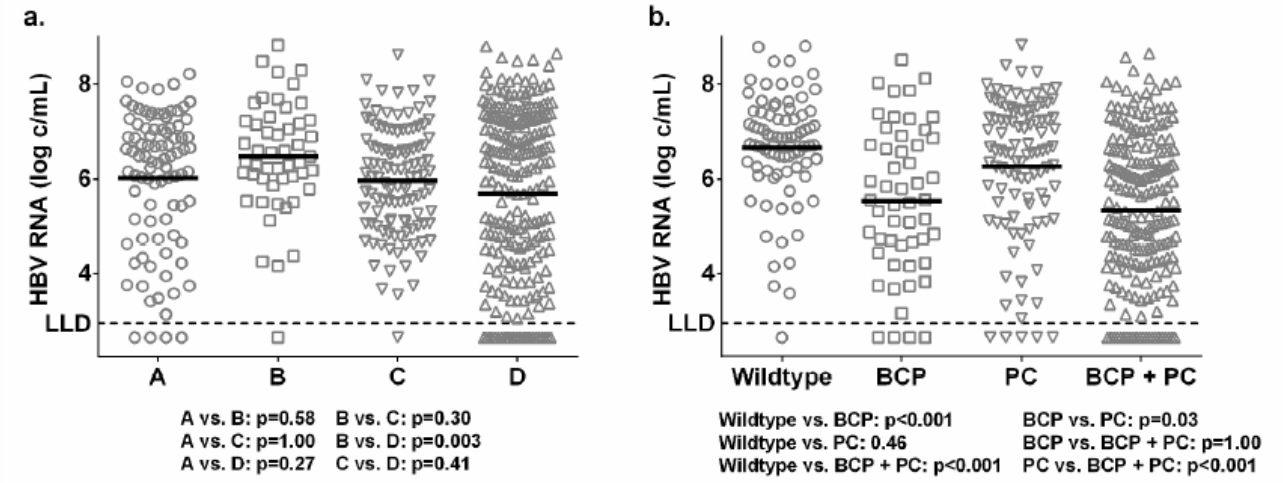


Serum HBV-RNA levels have the highest accuracy for distinguishing mild (score <2) from severe liver histopathology at 2.45 log10 copies/ml (PPV 80% NPV 89%)

Wang et al. Journal of Hepatology 2018 vol. 68 j 16–24

HDV RNA levels are influenced by several factors





van Campenhout et al. Hepatology 2018, doi: 10.1002/hep.29872

Summary

- HBV DNA, HBeAg and HBsAg remain the most important diagnostic marker
  - L-HBs may be a better marker than total HbsAg
- Current markers do not reflect the acitivity of cccDNA
- HBV RNA and HBcrAg emerge as valuable markers, which need further validation