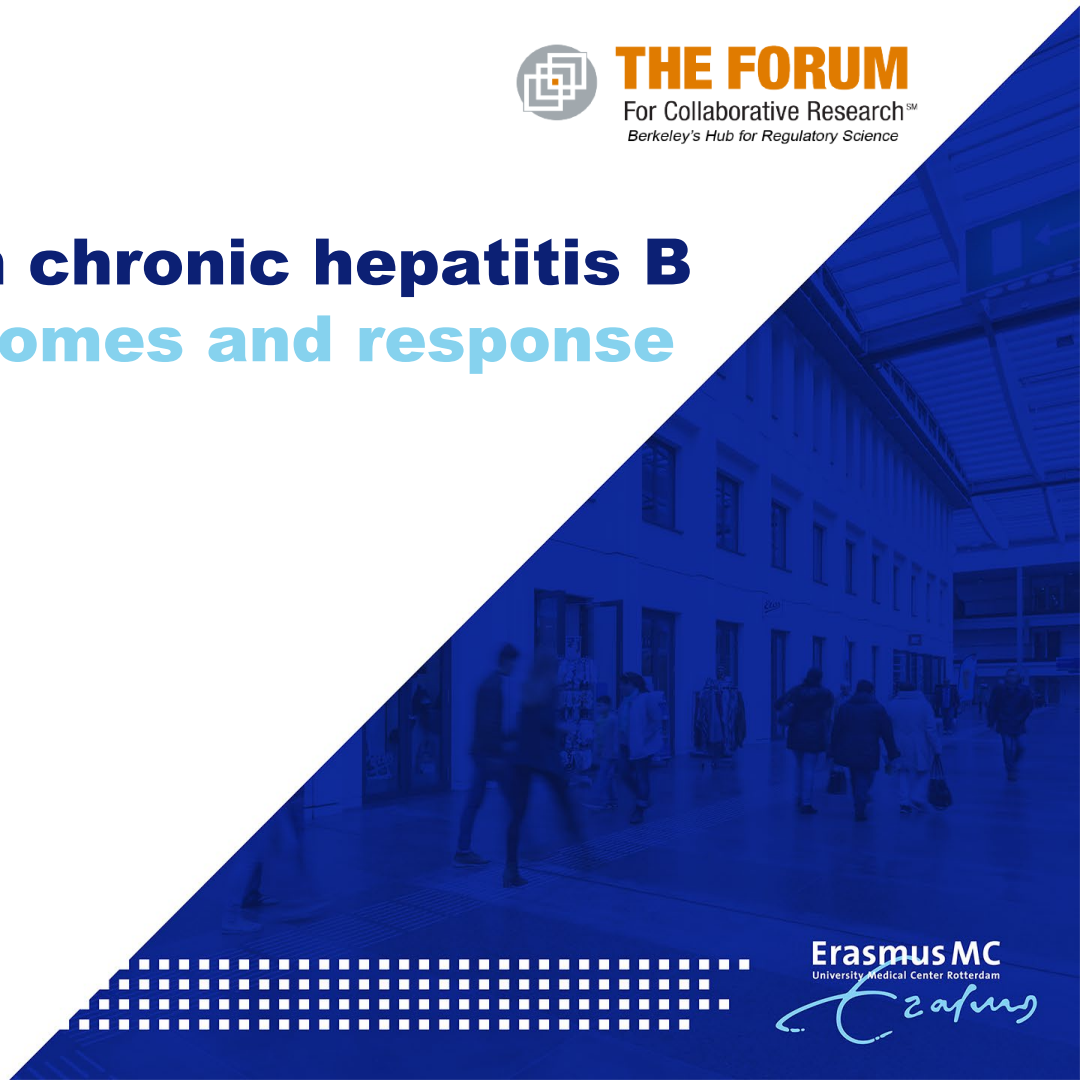
HBV FORUM 14 MEETING

THE FORUM
For Collaborative Research℠
Berkeley's Hub for Regulatory Science

MASLD in patients with chronic hepatitis B

Impact on clinical outcomes and response to antiviral therapy



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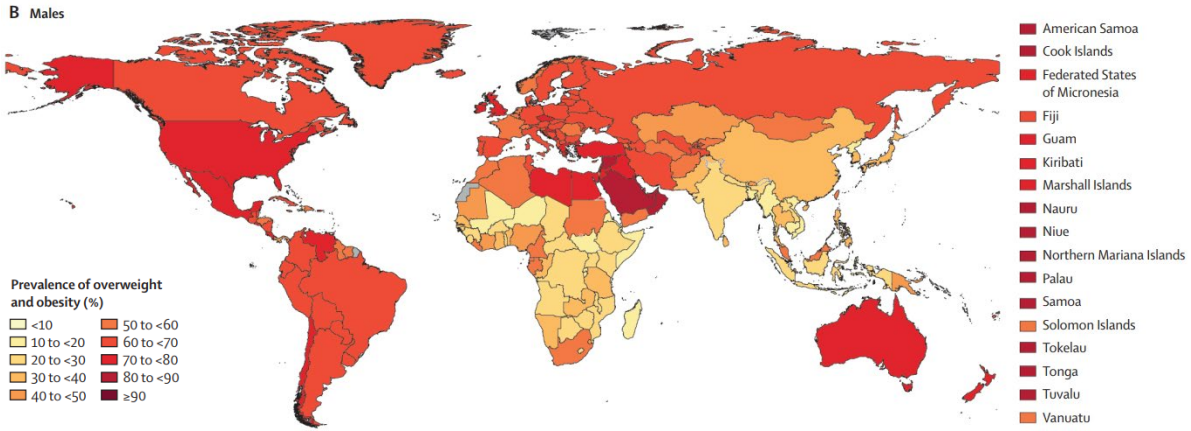
Disclosures

Potential COI	
Research grants	Gilead Sciences, Vir, Roche, GSK, Fujirebio
Advisory boards	Gilead Sciences, Fujirebio, Vir, Albireo/Ipsen

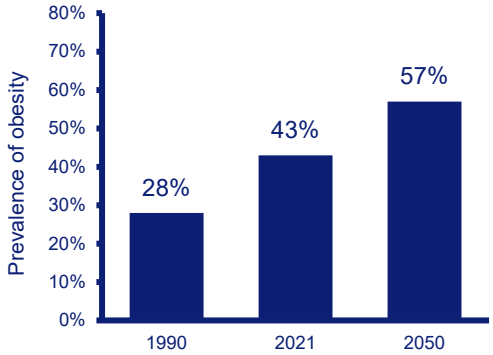
Epidemiology

The metabolic syndrome pandemic

Increasing prevalence of obesity accross the globe



Global prevalence of obesity



GBD Investigators, Lancet 2025

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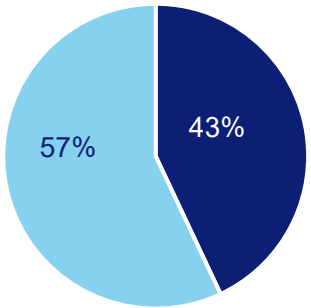
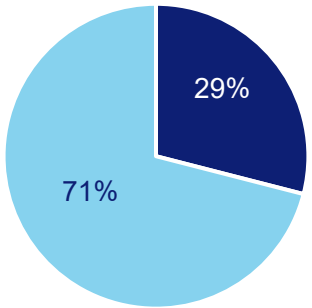
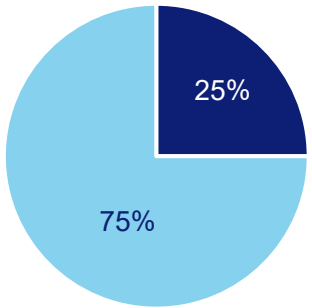
The metabolic syndrome pandemic

Prevalence of metabolic comorbidities in adults



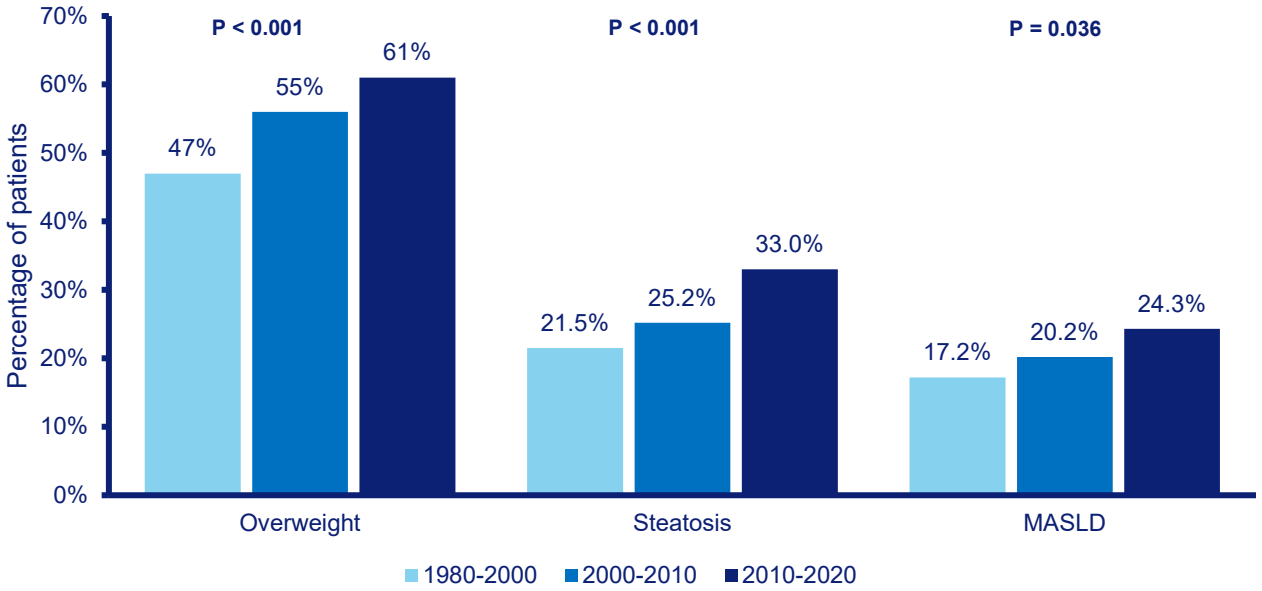




Noubiap, Diab Res and Clin Prac 2022

Chronic hepatitis B and metabolic comorbidities

An increasingly common combination – data from NL



MASLD = steatotic liver disease + ≧1 metabolic comorbidity

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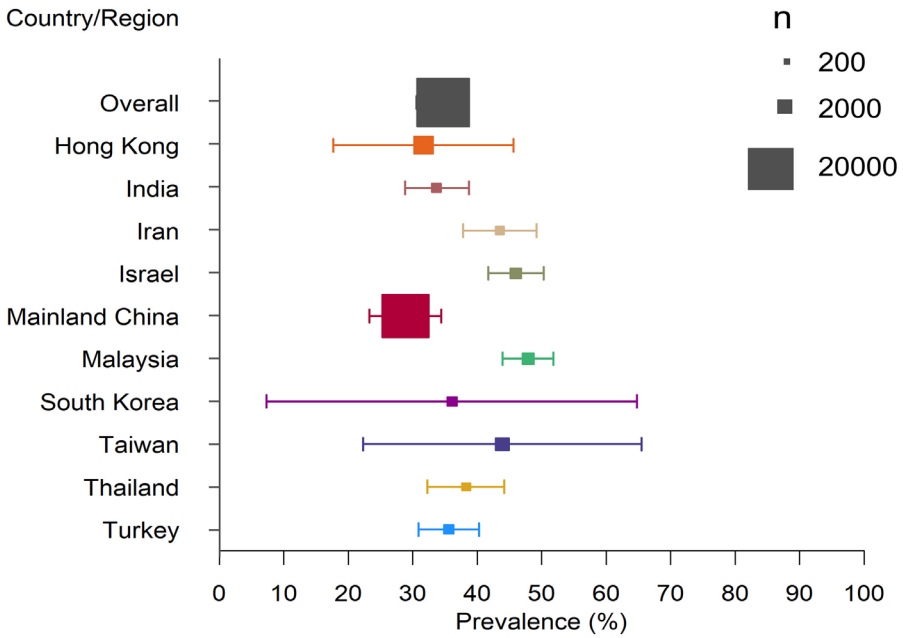
Van der Spek et al, Eur J Internal Med 2023.

Chronic hepatitis B and steatotic liver disease

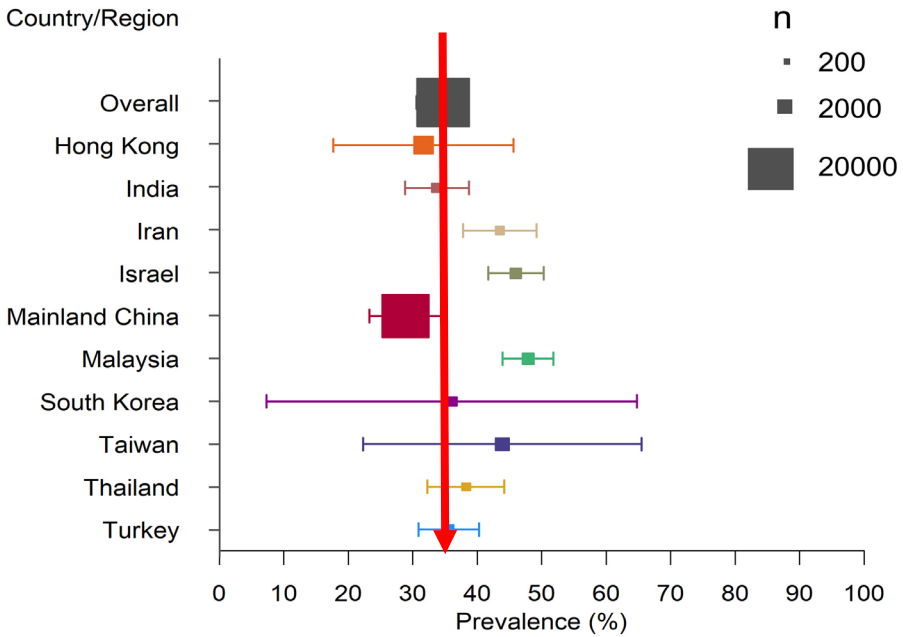
An increasingly common combination – global data



Yang, Liver International 2022

Chronic hepatitis B and steatotic liver disease

An increasingly common combination – global data

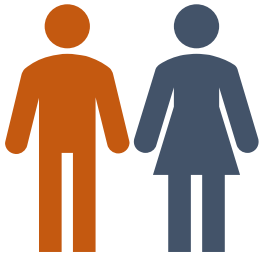


Yang, Liver International 2022

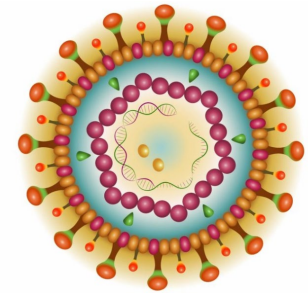
Impact of metabolic comorbidities and MASLD on the natural history of CHB

CHB patients with MASLD

Demographics and virological characteristics



- Older
- More frequently men
- More metabolic comorbidities



- Higher ALT
- Negative HBeAg
- Lower HBV DNA
- Lower HBV RNA
- Lower HBsAg

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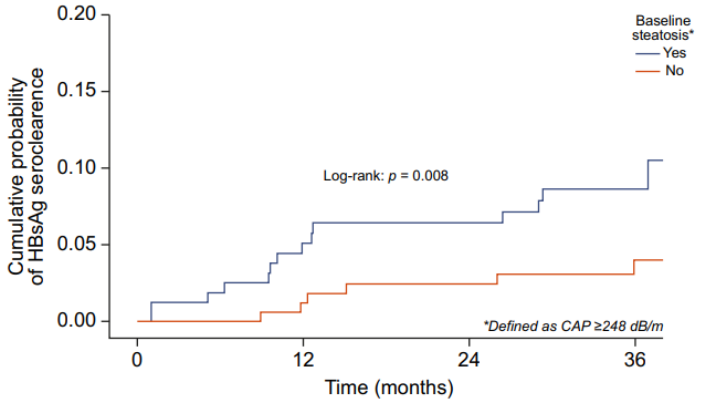
Choi, Hepatology 2020; van Kleef JHEP Report 2021; Yi Virology Journal 2024; Huang, J Hepatol 2025; Yang, Liver Int 2022

Steatotic liver disease in CHB

Association with spontaneous HBsAg clearance

Prospective follow-up study of 330 treatment naive CHB patients with normal ALT and low HBVDNA in Hong Kong

Characteristics	N=330
Age, years	51
Male	41%
Metabolic syndrome	31%
HBV DNA (IU/mL)	189
qHBsAg (log IU/mL)	5.2
CAP (dm/m)	246
Liver stiffness (kPa)	4.8



- Patients with steatosis were older, had lower HBsAg
- Steatosis independently associated with HBsAg clearance

Mak, J Hepatol 2020

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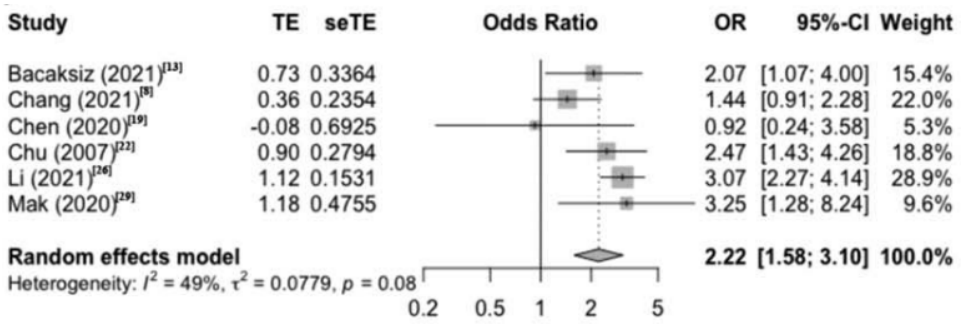
Steatotic liver disease in CHB

Association with spontaneous HBsAg clearance

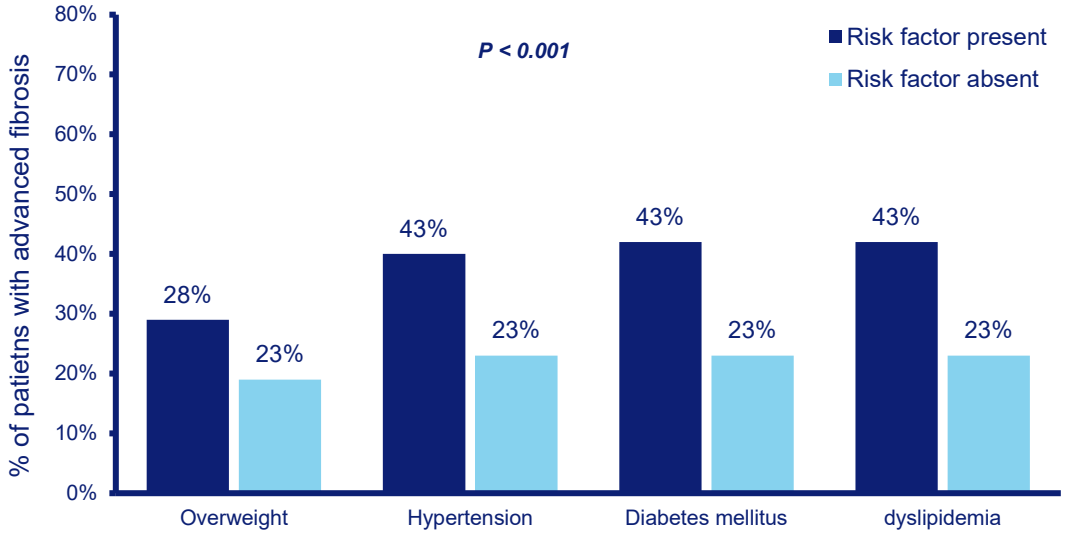
- Systematic review and meta-analysis
- 6 studies, 3870 patients (47% steatosis)
- Steatosis significantly associated with HBsAg clearance (OR 2.2, p<0.001)



Mao, Hepatology 2022

Metabolic dysfunction in CHB

Higher risk of advanced fibrosis



Van Velsen, CGH 2025

Metabolic dysfunction in CHB

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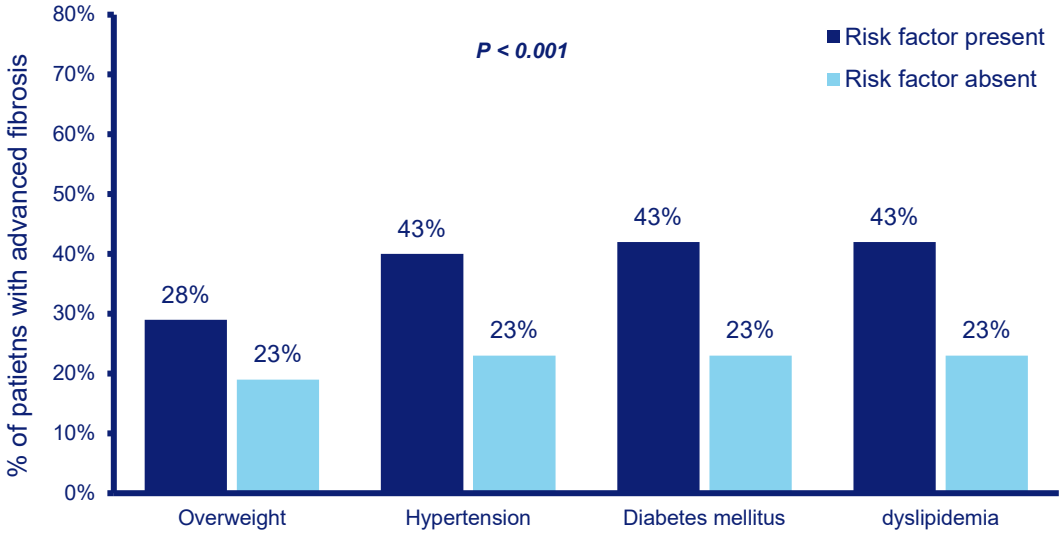
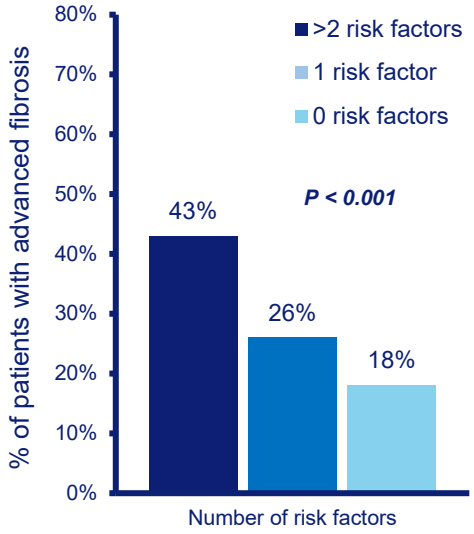




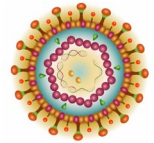
Van Velsen, CGH 2025

MASLD in patients with CHB

Higher risk of adverse liver-related outcomes

n = 780

n = 296



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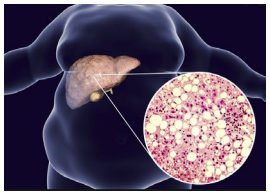

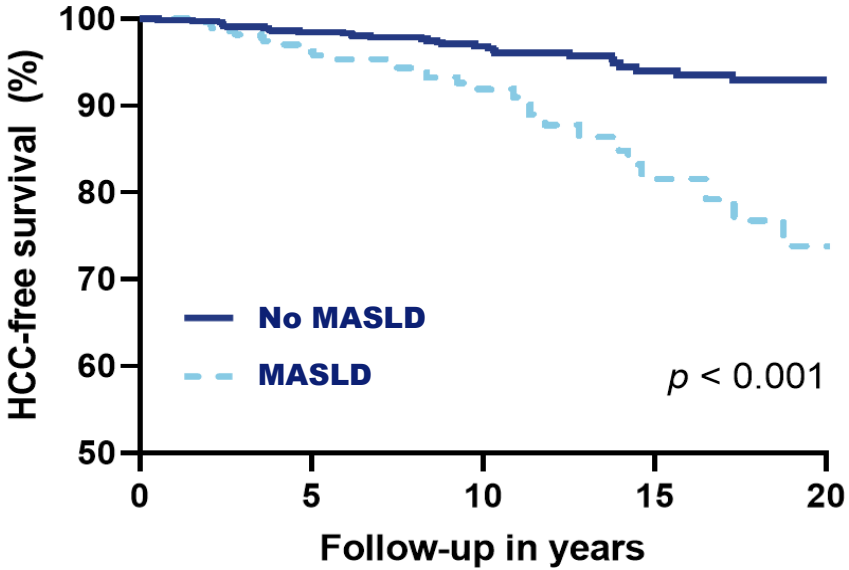

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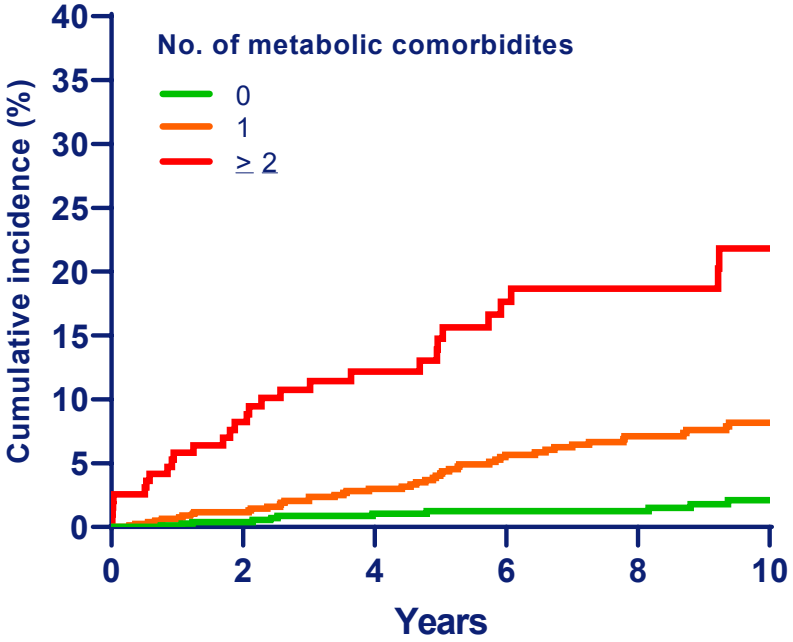
Van Kleef, JHEP Reports 2021; Choi et al, Hepatology 2020

HBV and metabolic dysfunction

Increased risk with higher metabolic burden

Long-term follow-up study of 1850 CHB patients from the Netherlands and Canada

Characteristics	N=1850
Age, years	37 (28-47)
Ethnicity, n (%)	
Caucasian	749 (40.5)
Asian	779 (42.1)
Other	322 (17.4)
Cirrhosis, n (%)	186 (10.1)
Diabetes, n (%)	82 (4.4)
Dyslipidemia, n (%)	116 (6.3)
Hypertension, n (%)	161 (8.7)
Overweight, n (%)	926 (50.1)
Events, n (%)	111 (6.0)
HCC	71 (3.8)
Ltx	43 (2.3)
Liver-related death	42 (2.3)



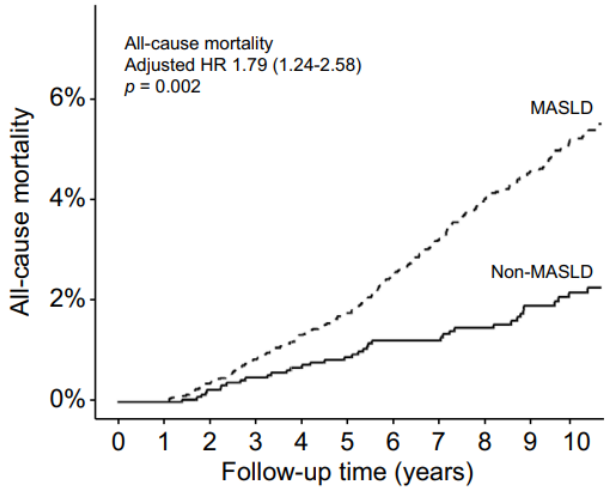
Patmore, CGH 2023

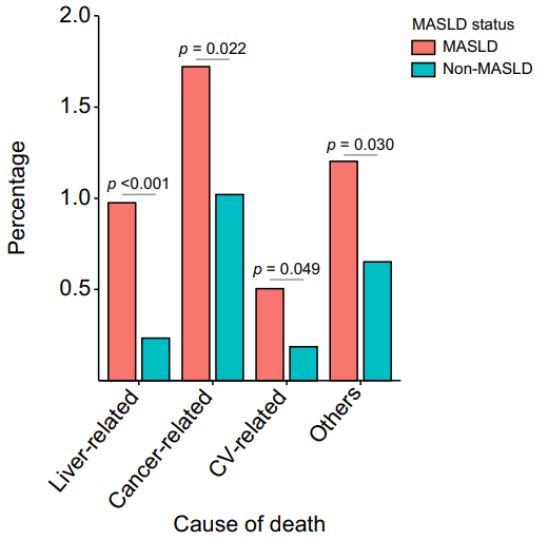
HBV and metabolic dysfunction

MASLD is associated with excess mortality

Study

- 8718 CHB patients with steatotic liver disease
- 6562 had MASLD
- Median follow-up 9.1 years
- Endpoints: all-cause and cause-specific mortality





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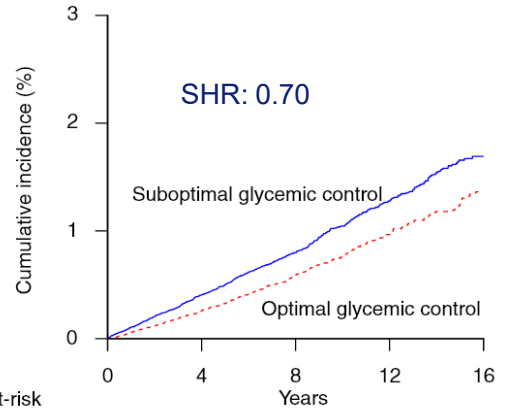
Huang, J Hepatol 2025

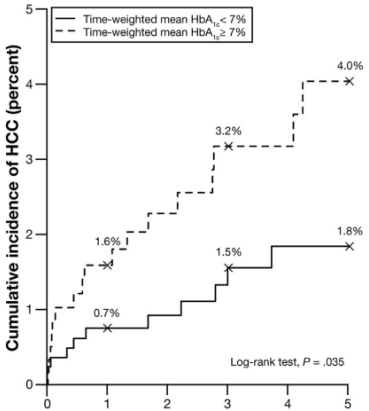
Treatment of diabetes mellitus
Impact on HCC risk

Diabetes mellitus alone



Number of at-risk					
Suboptimal control	73,215	54,952	29,717	13,675	2,031
Optimal control	73,215	58,305	30,812	13,407	2,267

Diabetes mellitus + CHB



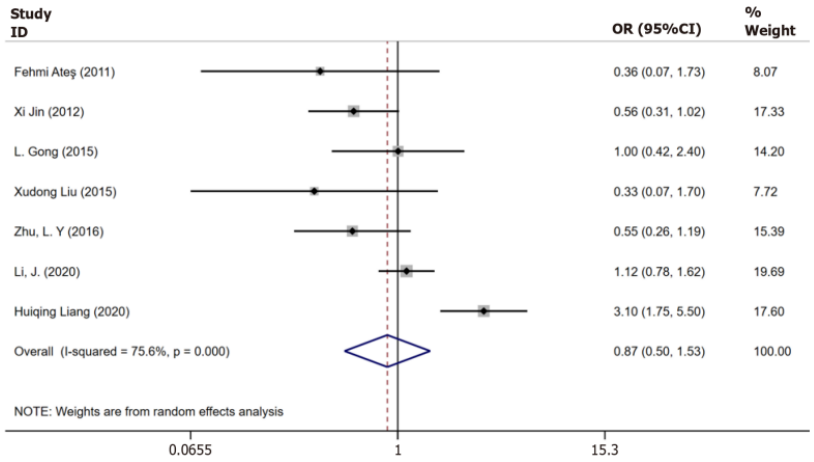
Number at risk						
Time-weighted mean HbA1c < 7%	843	681	558	431	324	241
Time-weighted mean HbA1c ≥ 7%	612	463	366	293	236	180

Mao, AP&T 2024; Yip, CGH 2018

Impact on response to antiviral treatment

Steatotic liver disease in CHB patients on NUCs
Influence on virological and biochemical response

HBV DNA suppression

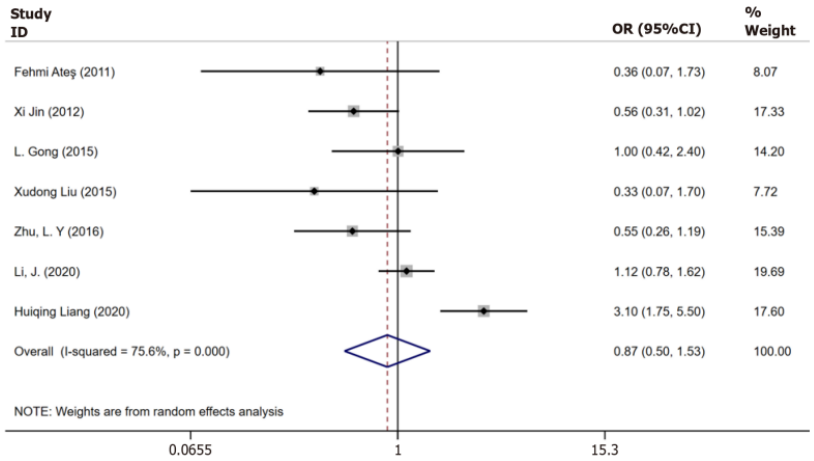


Liu, WJH 2024

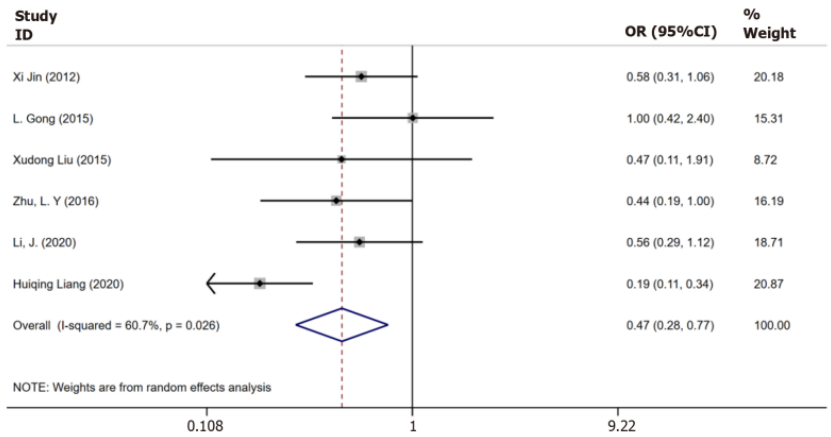
Steatotic liver disease in CHB patients on NUCs

Influence on virological and biochemical response

HBV DNA suppression



ALT normalisation



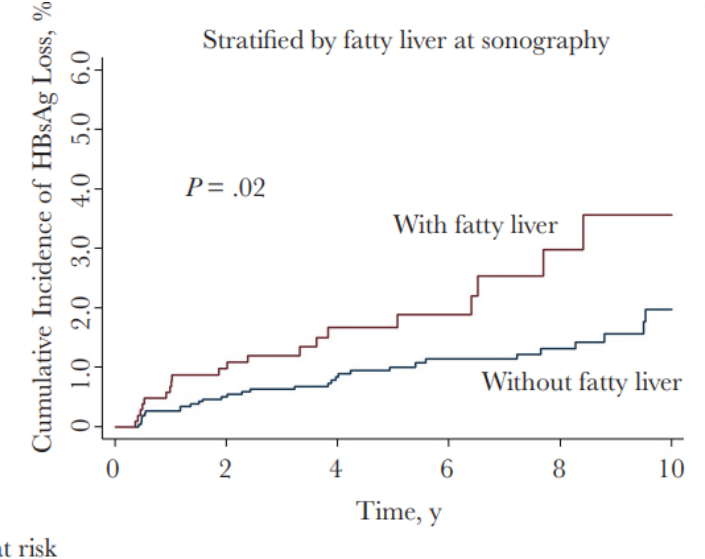
Liu, WJH 2024

Steatotic liver disease in CHB patients on NUCs

Influence on virological and biochemical response

Prospective follow-up study of 4769 CHB patients from around the globe who received antiviral therapy with entecavir or tenofovir

Characteristics	N=4769
Age, years	50
Male	69%
Diabetes mellitus	9%
Hyperlipidemia	13%
Alcohol use	15%
Fatty liver (imaging)	28%
ETV / Tenofovir	100%

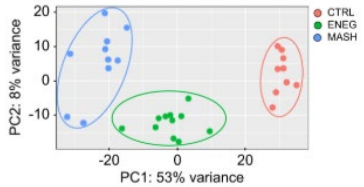


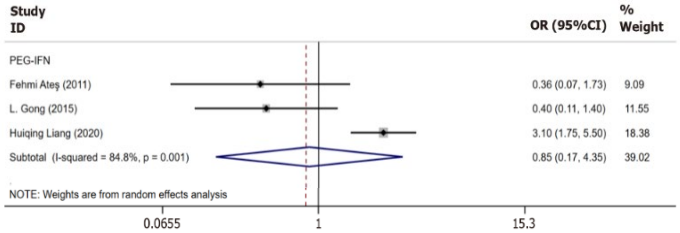
Hsu, JID 2021

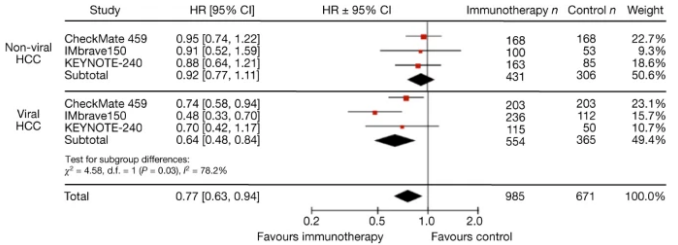
Steatotic liver disease in CHB

Influence on response to immunomodulators

- Presence of MASH reduces IFN and macrophage gene signatures
- Association with response to IFN in CHB is unclear
- MASH limits anti-tumor surveillance and HCC tumor response to anti-PDL1 therapy







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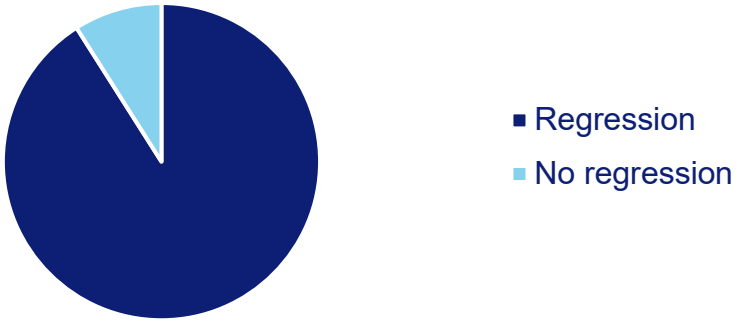
Osmani, J Hepatol 2025; Liu, WJH 2024; Pfister, Nature 2021

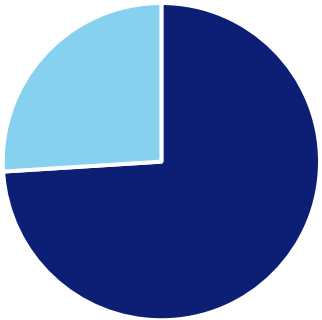
Antiviral therapy for CHB

Improvement of histology after 5 years of TDF

91% regression of fibrosis



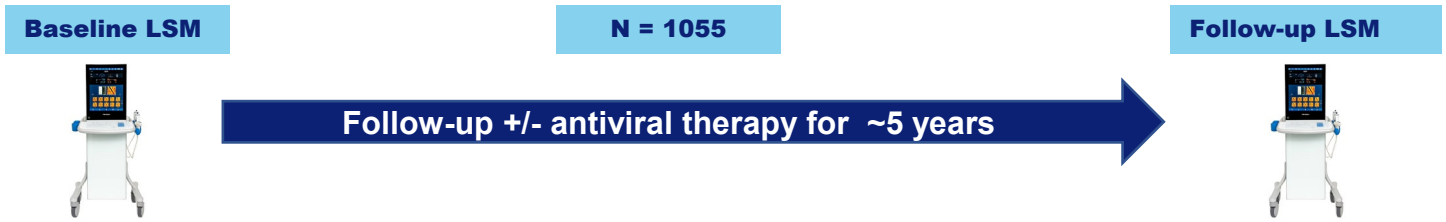
74% regression of cirrhosis



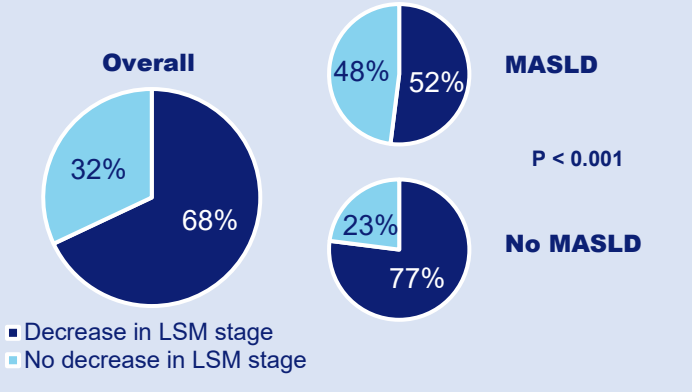
Marcellin, Lancet 2013.

MASLD in patients with CHB

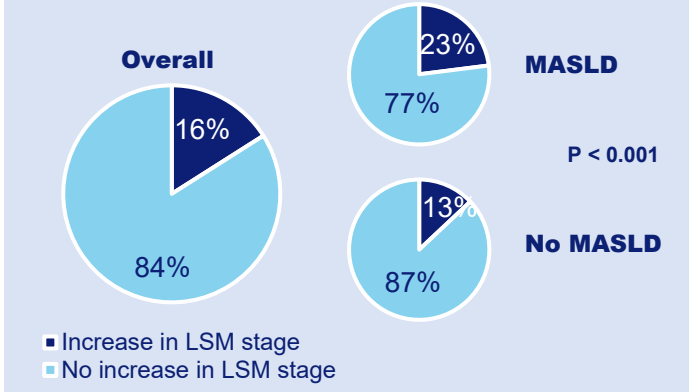
Less LSM decline, more LSM increase



LSM decrease



LSM increase



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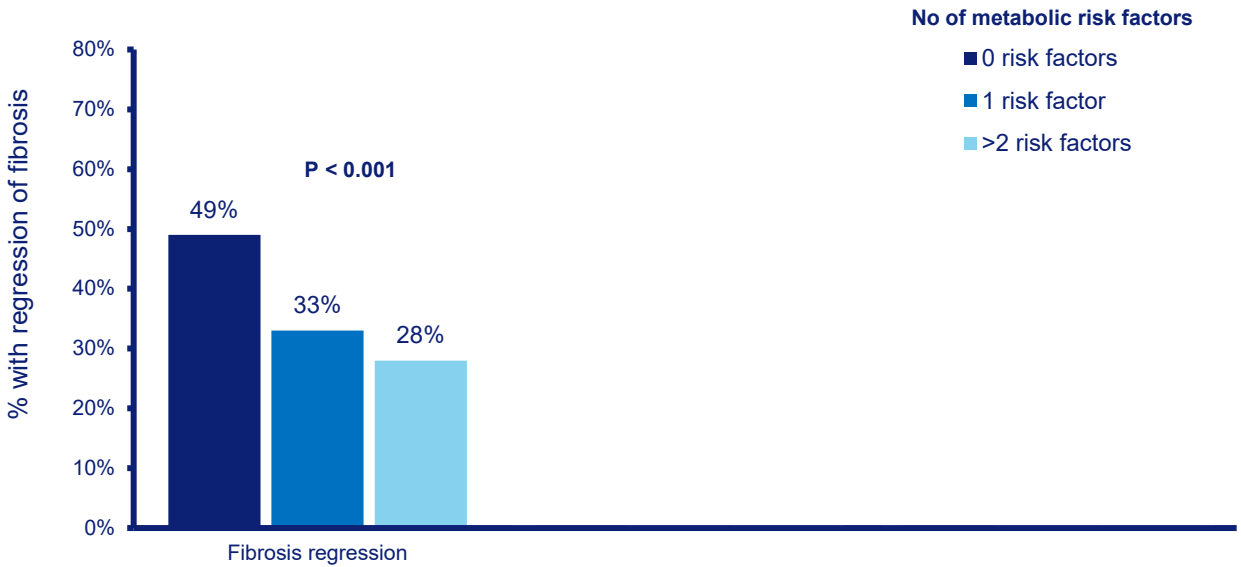
Patmore, Liver Int 2025

Metabolic comorbidities in CHB

Less fibrosis regression with antiviral therapy

Study

- N=1307 CHB patients from 8 RCTs and 2 academic hospitals
- All underwent liver biopsy at baseline and 48-72 weeks after treatment initiation
- Metabolic risk factors assessed
  - Overweight
  - Diabetes mellitus
  - Dyslipidemia
  - Hypertension



Metabolic risk factors: overweight, diabetes, hypertension, dyslipidemia

Van Velsen, CGH 2025

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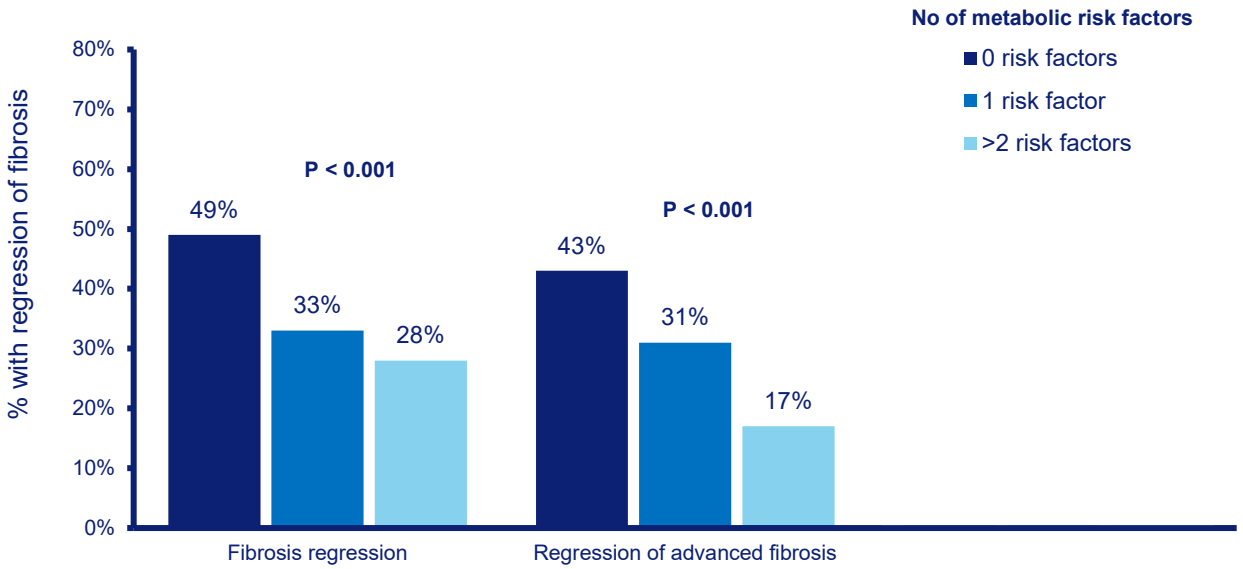

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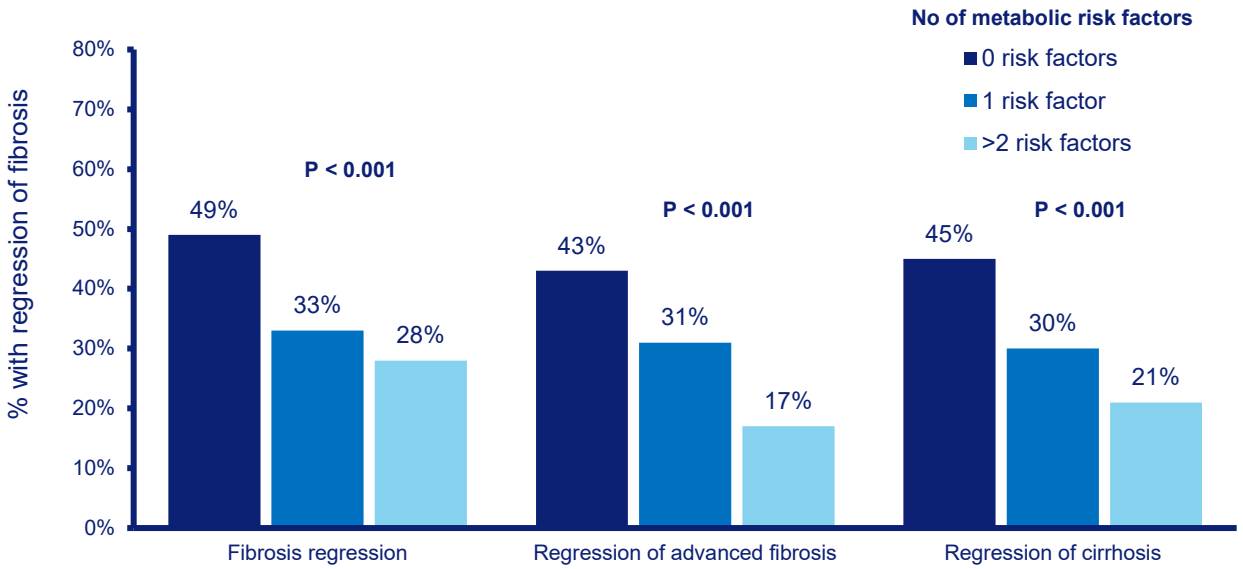

Metabolic risk factors: overweight, diabetes, hypertension, dyslipidemia

Van Velsen, CGH 2025

Metabolic comorbidities in CHB

More fibrosis progression despite antiviral therapy

Study

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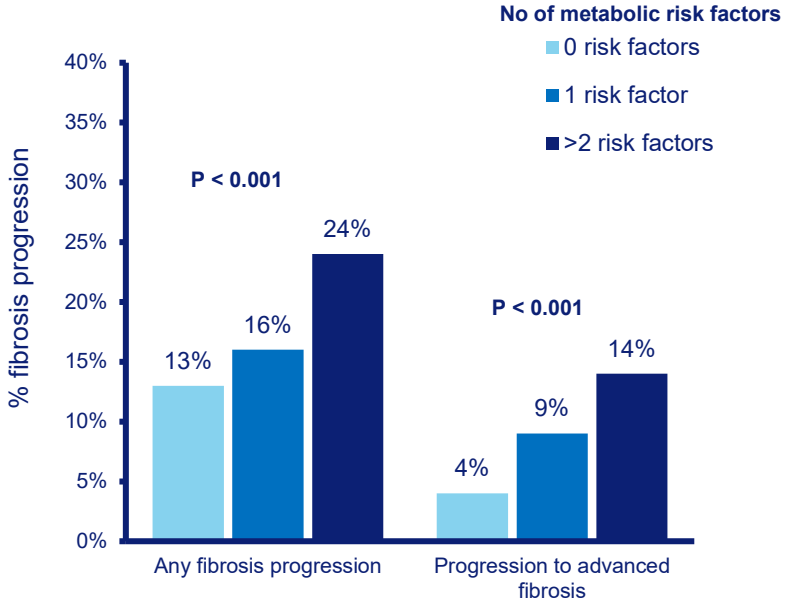
- All underwent liver biopsy at baseline and 48-72 weeks after treatment initiation
- Metabolic risk factors assessed
  - Overweight
  - Diabetes mellitus
  - Dyslipidemia
  - Hypertension



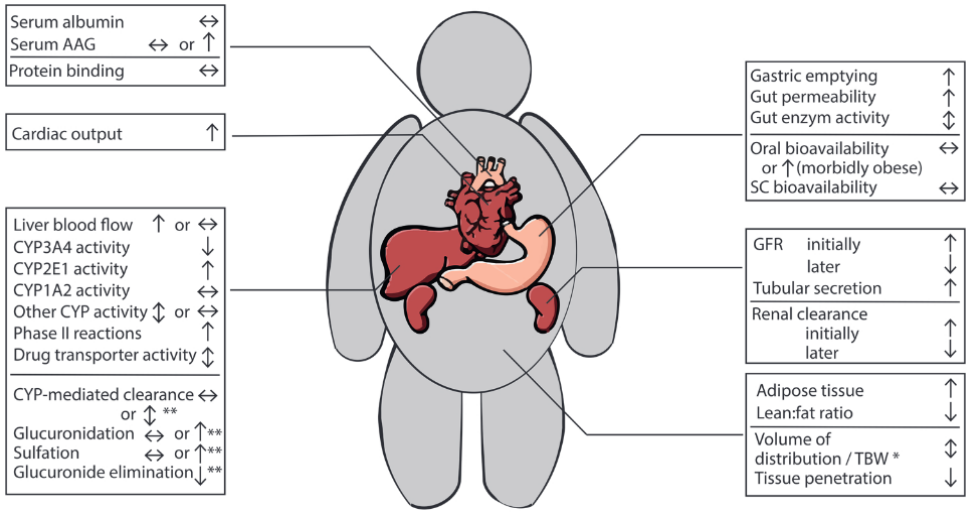
Metabolic risk factors: overweight, diabetes, hypertension, dyslipidemia

Van Velsen, CGH 2025

Potential implications for drug development

Potential implications for drug development

Pharmacokinetics and pharmacodynamics



The model used for the study	Duration of study	Transporter expression	
		Protein	mRNA
Methionine-choline-deficient (MC-) diet and high fat diet in rats	8 weeks	↓ OATP1A1 ↓ OATP1B2	↓ NTCP ↓ OATP1A1 ↓ OATP1A4 ↓ OATP1B2 ↓ OAT2 ↓ OAT3
Zucker rats	8-weeks-old	↓OATP2 ↓NTCP ↓MRP2	↓ OATP2 ↓ MRP2 ↓ NTCP × Oatp1 × Mrp3 × Mrp4 × BSEP × BCRP
Fatty human liver samples	–	↑MRP1 ↑MRP3 ↑MRP4 ↑MRP5 ↑MRP6 ↑MDR1 ↑ABCG2	↑ABCC1 ↑ABCC4 ↑ABCC3 ↑ABCC5 ↓ABCC6 ↑ABCB1 ↑ABCG2 × ABCC2
Methionine- and choline-deficient	8 weeks		↑MRP1 ↑MRP4 ↑MRP5 ↓ NTCP, ↓ OATP1A1 ↓OATP1B2
Patient with NASH	–	↓NCTP	↑NTCP
Patient with NAFLD	–	↓BSEP	↓BSEP

Smit, Exp Opn on Drug Met & Tox 2018; Laddha, Mol Basis Disease 2024

Potential implications for drug development
Drug-drug interactions and side-effects

- Drug-drug interactions with medication used for metabolic comorbidities
- Class specific side-effects (e.g. thrombocytopenia) of anti-HBV therapies can be relevant for patients with specific conditions (e.g. those taking antiplatelet drugs)
- Sequelae of ALT flares may be more severe in patients with an underlying chronic liver disease like MASLD

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Smit, Exp Opn on Drug Met & Tox 2018; Laddha, Mol Basis Disease 2024;

Potential implications for drug development
Treatment efficacy

- MASLD can influence biochemical response
  - Important when ALT is used as response or safety endpoint
- MASLD might influence HBsAg loss rates in untreated and NUC treated patients
  - Can therefore influence ‘background’ rates of HBsAg loss
  - Relevant for sample size calculation and comparisons of HBsAg loss rates accross cohorts
- MASLD could influence response to immunomodulators like IFN and checkpoint inhibitors
  - Implications for patient selection
- Patients with MASLD have a persistent risk of adverse liver-related outcomes despite virological response
  - Especially relevant when using surrogate endpoints

Steatotic liver disease and HBV

Enrolment criteria in completed trials

Name	Phase	Primary endpoint	Fibrosis / Biochemical/ clinical endpoints	Other liver disease criteria	Metabolic comorbidity criteria
B-Clear	2b	HBsAg loss	Biochemical response	moderate-severe liver disease other than chronic HBV	uncontrolled hypertension, uncontrolled diabetes
PIRANGA	2	HBsAg loss		Clinically significant liver disease other than CHB	
REEF-1	2	% meeting withdrawal criteria (includes ALT <3xULN)	ALT	LSM <9	'medically stable' BMI <35
REEF-2	2b	HBsAg loss	ALT	Evidence of liver disease of non-HBV etiology	'medically stable' BMI <35

Erasmus MC

Agarwal J Hepatol 2024; Yuen, Lancet gastroHep 2023; Yuen NEJM 2022; Hou, NEJM 2024

Steatotic liver disease and HBV

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Steatotic liver disease and HBV

Enrolment criteria in ongoing trials

NCT	Phase	Primary endpoint	Secondary endpoints that might be influenced by MASLD?	Other liver disease criteria	Metabolic comorbidity criteria
NCT05630807	3	HBsAg loss	-	Moderate-severe non-HBV liver disease	uncontrolled hypertension, uncontrolled diabetes
NCT05970289	2	HBsAg loss	-	History of chronic liver disease other than HBV	BMI <32
NCT04856085	2	HBsAg loss	-	History of chronic liver disease other than HBV	
NCT06537414	2b	HBsAg loss	-	moderate-severe liver disease other than chronic HBV	uncontrolled hypertension, uncontrolled diabetes
NCT06550128	2	HBsAg loss	-	severe non-alcoholic fatty liver disease	BMI <32
NCT06491563	2	HBsAg loss	Biochemical response	History of chronic liver disease from any cause other than chronic HBV infection	BMI <32

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Steatotic liver disease and HBV

Enrolment criteria in ongoing trials

NCT	Phase	Primary endpoint	Secondary endpoints that might be influenced by MASLD?	Other liver disease criteria	Metabolic comorbidity criteria
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NCT05970289	2	HBsAg loss	-	History of chronic liver disease other than HBV	BMI <32
NCT04856085	2	HBsAg loss	-	History of chronic liver disease other than HBV	
NCT06537414	2b	HBsAg loss	-	moderate-severe liver disease other than chronic HBV	uncontrolled hypertension, uncontrolled diabetes
NCT06550128	2	HBsAg loss	-	severe non-alcoholic fatty liver disease	BMI <32
NCT06491563	2	HBsAg loss	Biochemical response	History of chronic liver disease from any cause other than chronic HBV infection	BMI <32

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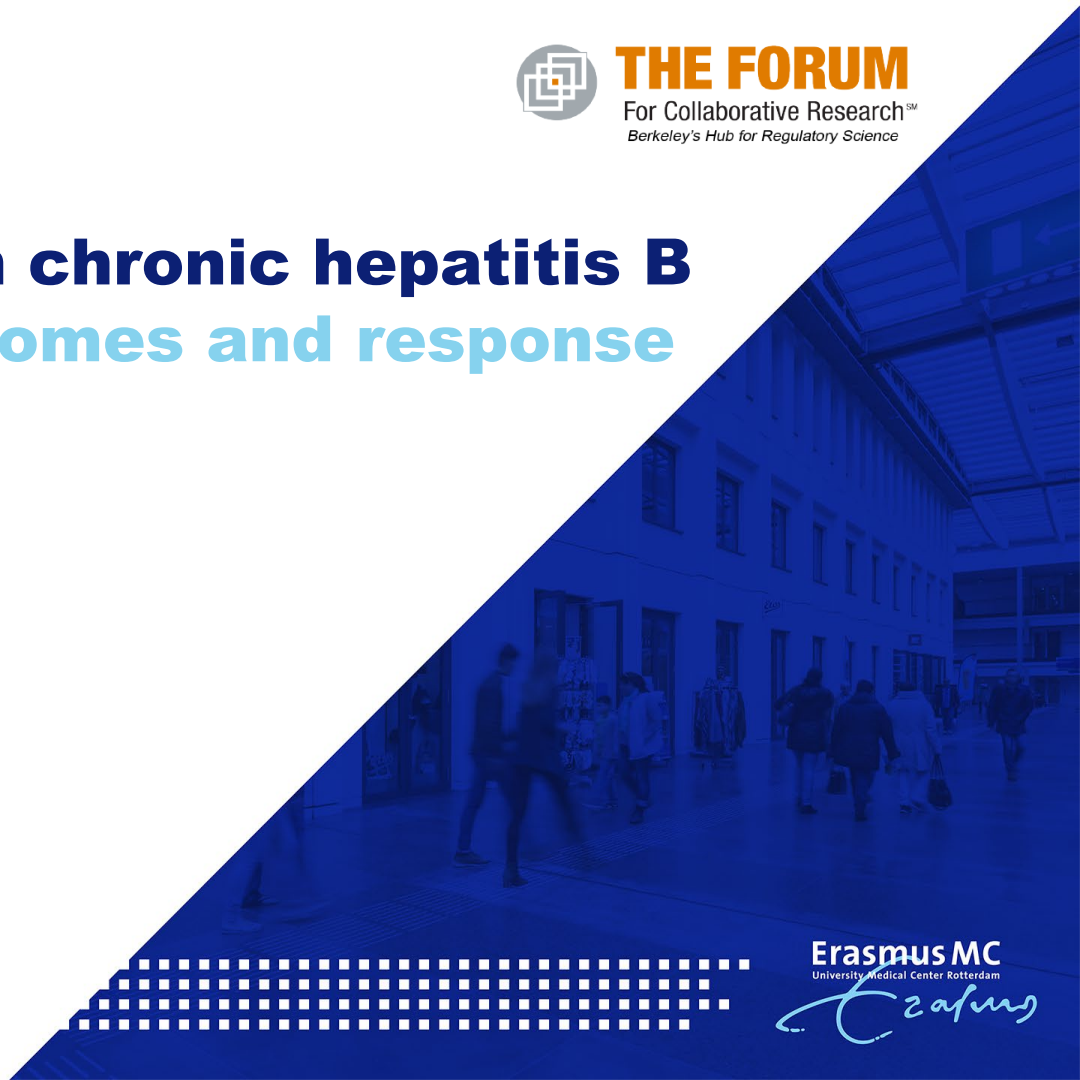
HBV FORUM 14 MEETING

THE FORUM
For Collaborative Research℠
Berkeley's Hub for Regulatory Science

MASLD in patients with chronic hepatitis B

Impact on clinical outcomes and response to antiviral therapy



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