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# NITs and Outcome

## Update from the International Liver Congress (ILC) 2022


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Eine strategische Allianz

# Conflict of interest

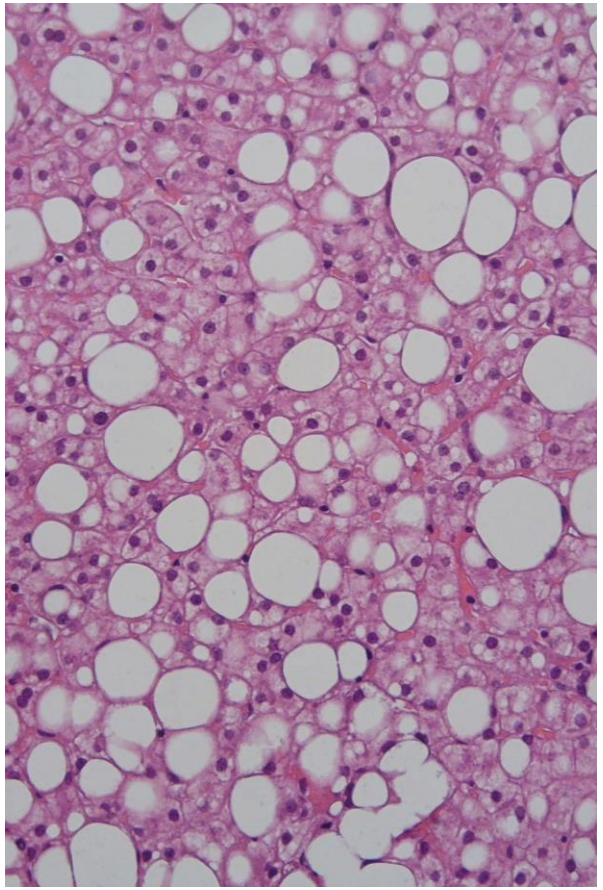
*Consulting advisor* for Apollo Endosurgery, Albireo Pharma Inc, Bayer, BMS, Boehringer Ingelheim, Echosens, Genfit, Gilead, GSK, Heel GmbH, Intercept, Ipsen, Inventiva Pharma, Julius Clinical, Madrigal, MSD, Nordic Bioscience, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi, Shinogi, Siemens Healthcare GmbH, & Summit Clinical Research

*Grant & research* support from Gilead, Boehringer Ingelheim, Nordic Bioscience, & Siemens Healthcare GmbH

*Speaker honorarium* from Boehringer Ingelheim & MedPublico GmbH.

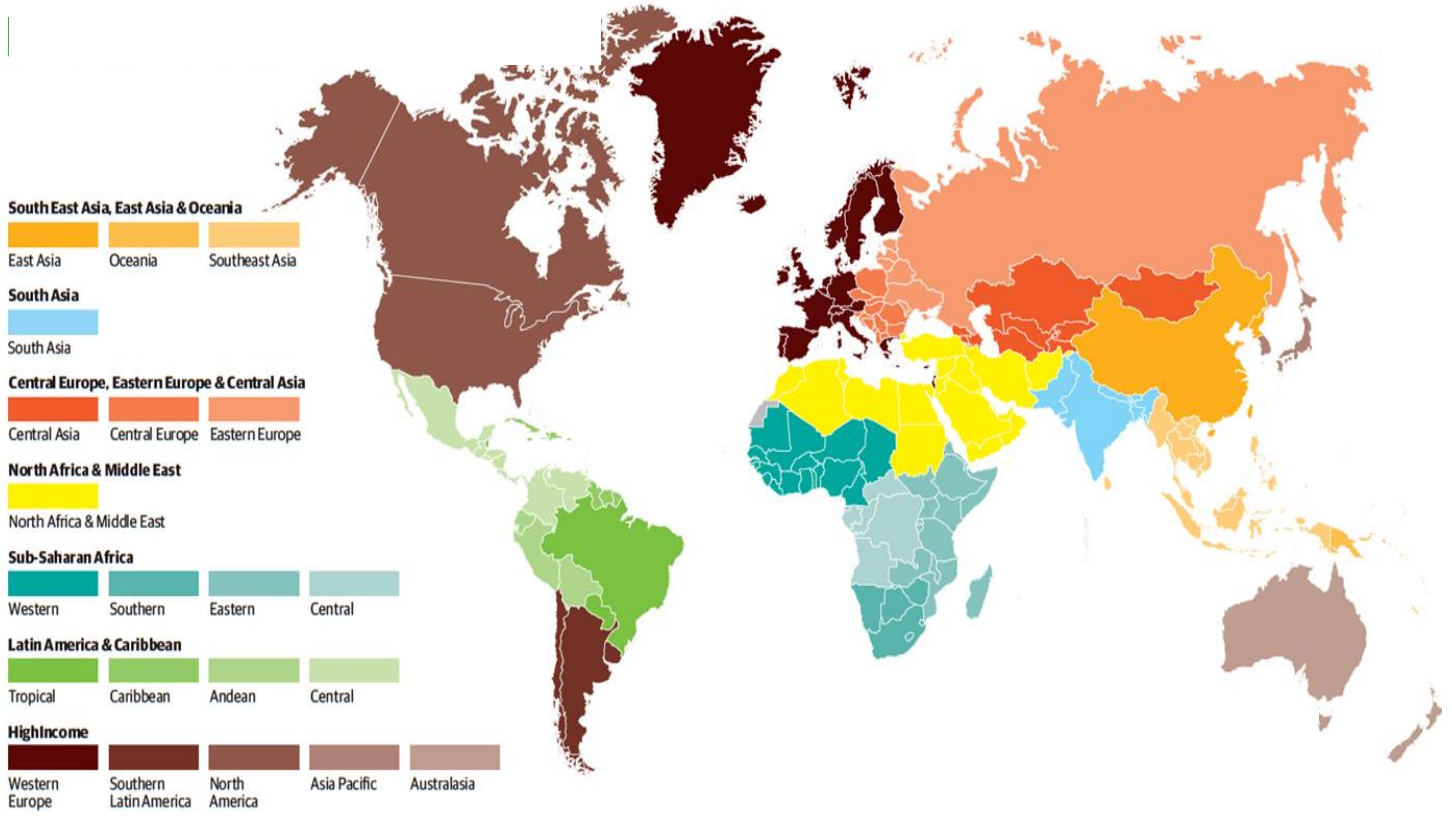
What's new following ILC 2022?

# PREVALENCE



# Global Burden of Disease (GBD)

## 21 GBD Regions




- ✓ GBD provides an assessment of prevalence, incidence morbidity (DALYs) and mortality for 369 diseases and injuries in 204 countries and territories (21 GBD regions) from 1990 to 2019

# Changing the face of liver disease

## HCC- and liver-associated mortality (2009 – 2019)

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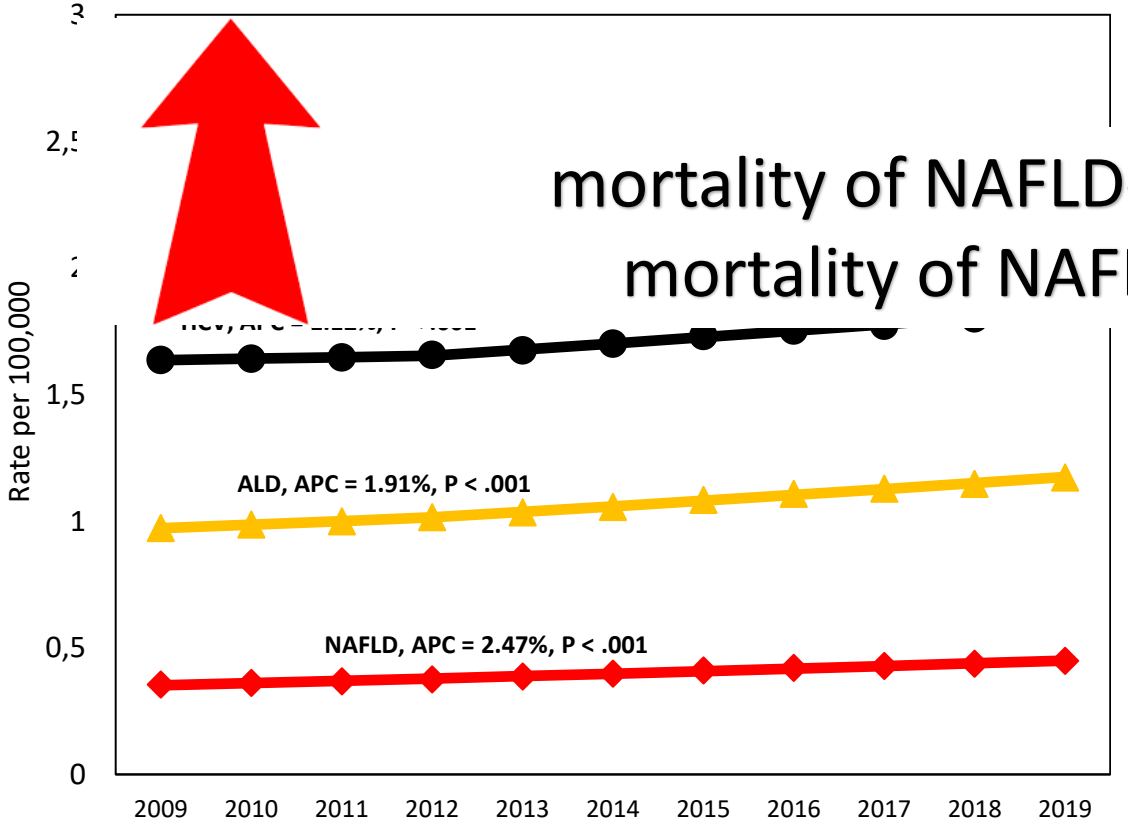
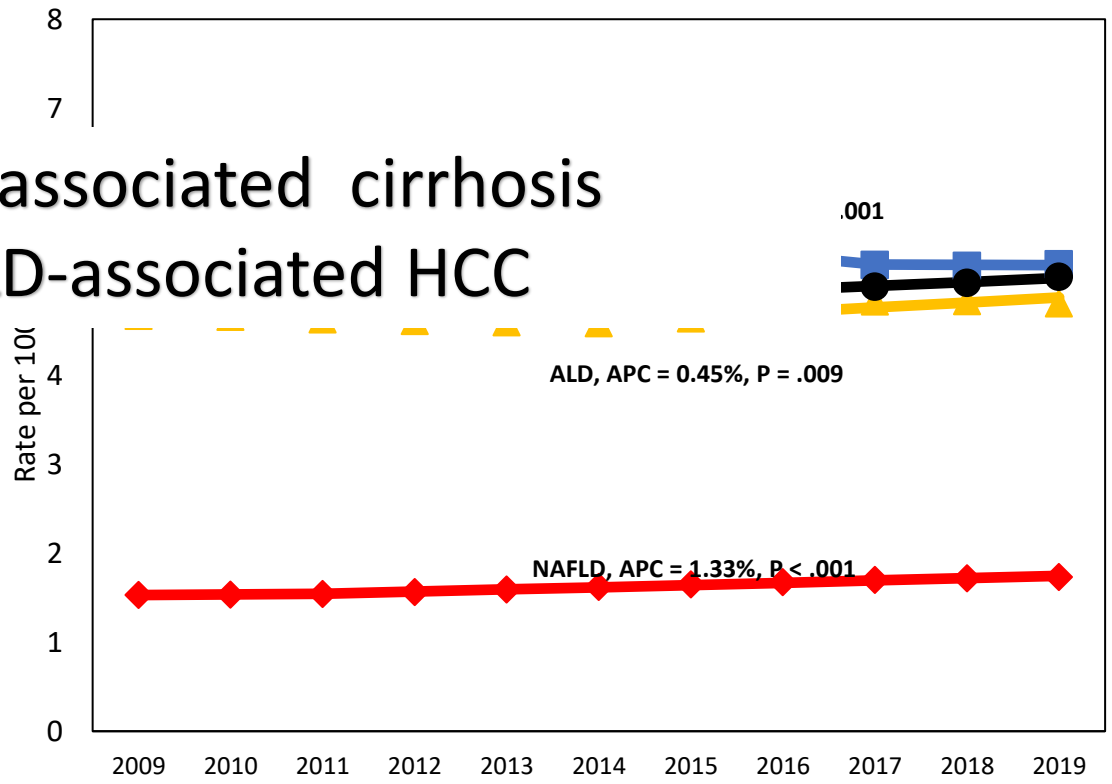
### Global Change in **Liver Cancer Death**




### Global Change in **CLD Death**




mortality of NAFLD-associated cirrhosis

mortality of NAFLD-associated HCC

OS025 Z. Younossi et al.

HEPATOLOGY COMMUNICATIONS, VOL. 0, NO. 0, 2022

# Prevalence and Risk Factors of Advanced Liver Fibrosis in a Population-Based Study in Germany

Yvonne Huber,[1] Andreas Schulz,[2] Irene Schmidtmann,[3] Manfred Beutel,[4] Norbert Pfeiffer,[5] Thomas Münzel,[6,7] Peter R. Galle,[1] Philipp S. Wild,[2,7,8] Karl J. Lackner,[9]* and Jörn M. Schattenberg [1,10]*

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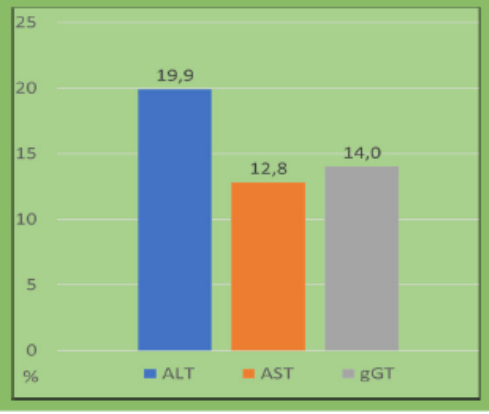
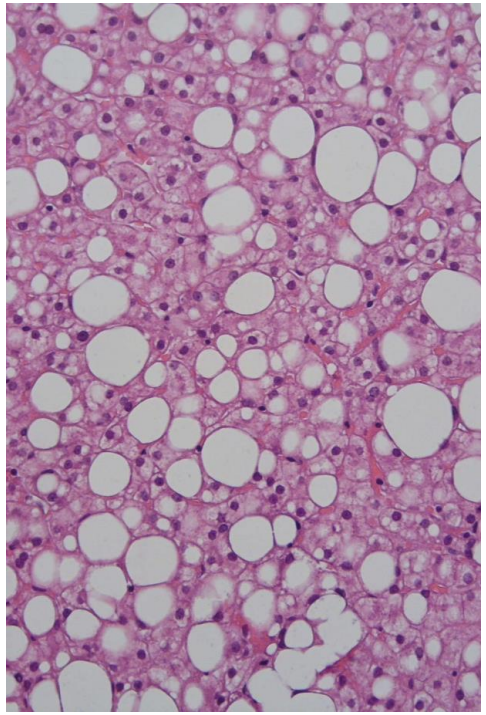
| Study Population | Findings |
|---|---|
| Population-based study (Gutenberg Health study) enrolled 2007 – 2012 **n = 14,950** | ➢ Frequency of elevated liver enzymes<br>  |
| | ➢ Hepatic steatosis: Positive FLI: 37.5%<br>➢ Advanced liver fibrosis:<br>➢ FIB-4 >2.67: 1.1%<br>➢ FIB-4 >1.3: 19.2%<br>➢ Male sex and age are risk factors for advanced fibrosis |

Huber, et al. *Hepatol Commun.*

HEPATOLOGY COMMUNICATIONS Open Access

Huber, Y. et al. Hepatol Commun. https://doi.org/10.1002/hep4.1899



What's new following ILC 2022?

# NIT‘S AND CLINICAL OUTCOME

# Linking FIB4 to outcome

## Prognostic Biomarker

**Study design**

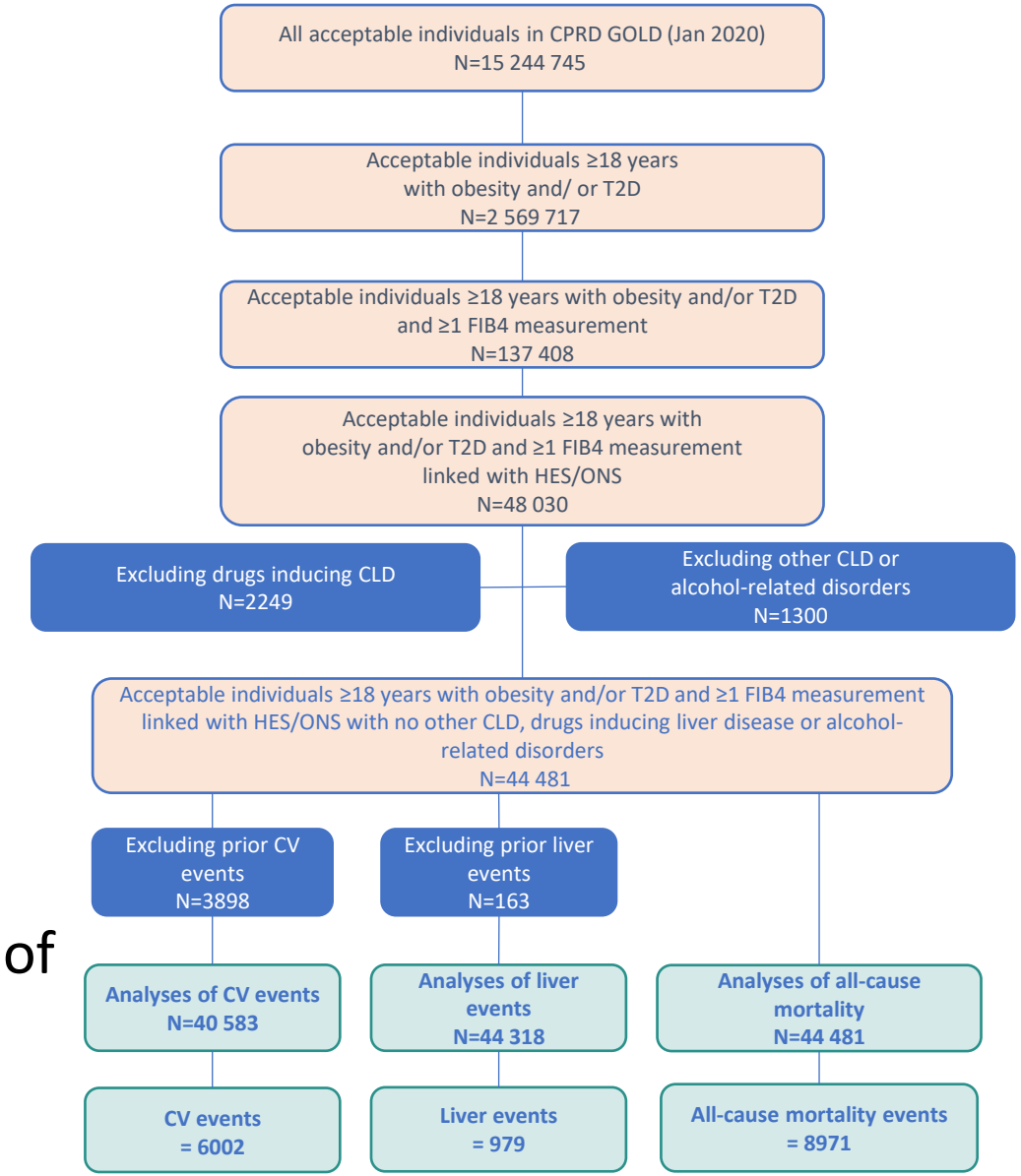
- Longitudinal non-interventional observational cohort study
- Country: UK
- Study period: 2001–2020
- Patients were followed from inclusion date* until time of first clinical event, database migration, 10 years after inclusion, or 1 January 2020 (whichever came first)
- FIB4 at inclusion was categorised as low (<1.30), indeterminate (1.30–2.67) or high (>2.67) risk

**Population**

- Male or female patients aged ≥18 years with obesity and/or T2D
- ≥1 FIB4 score calculable from CPRD
- No record of alcohol-related and/or other chronic liver disease registered in HES
- No prescriptions of drugs inducing liver disease registered in CPRD

**CPRD + Hospital Episode Statistics (HES) & Office for National Statistics (ONS)**

- The CPRD is a UK Government real-world research service
- It contains de-identified patient data from a network of General Practitioners across the UK
- General Practitioner medical records are linked to two other data sources in the current study: HES and ONS Death Registration Data




- ✓ UK – primary care
- ✓ Inclusion of overweight and/or T2D “at risk "of NASH population (16.9%)
- ✓ N= 44.481; Hepatic outcomes and mortality (close to 16.000 events)

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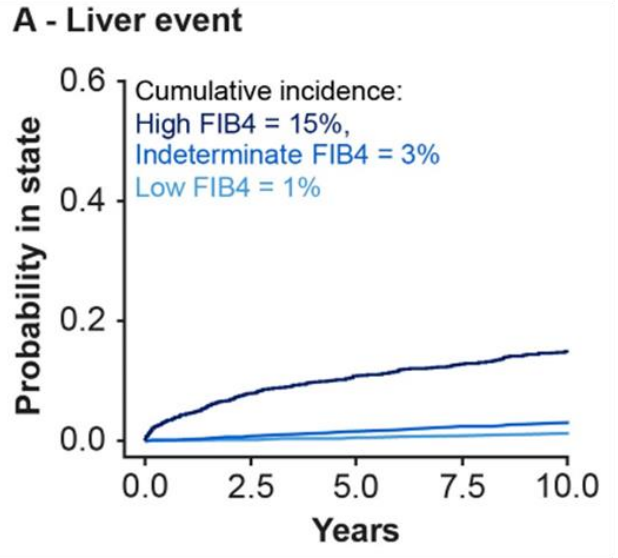
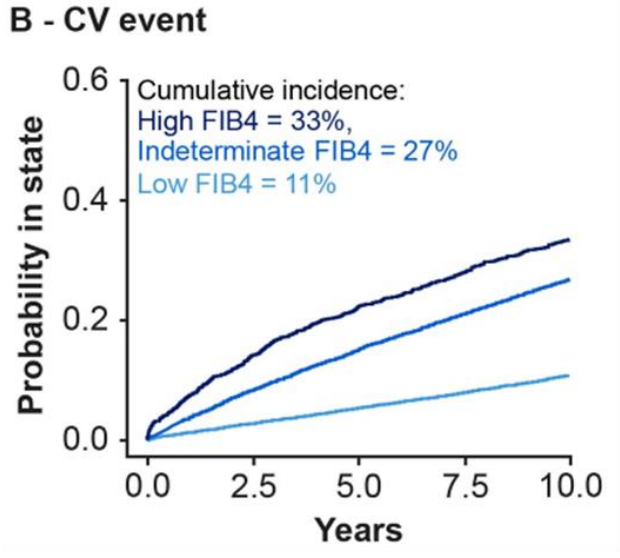
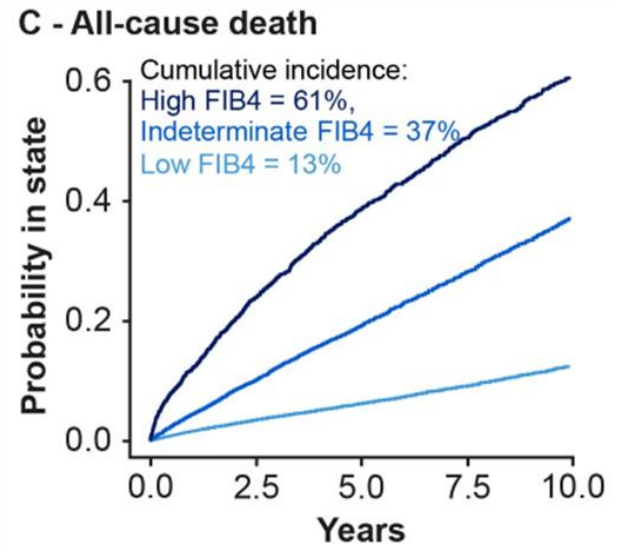
# Non-invasive test's -> FIB-4

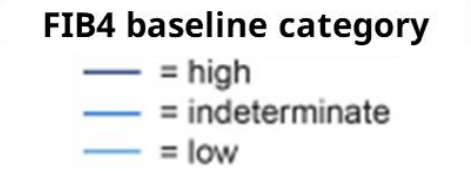
## Prognostic value



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# Morbidity and Outcome

## FIB-4 allows for risk stratification

| | Crude HR (95% CI) | Adjusted (age and sex) HR (95% CI) |
|---|---|---|
| **Liver events** | | |
| FIB4 low | 1.00 | 1.00 |
| FIB4 indeterminate | 2.81 (2.43, 3.26) | 2.45 (2.07, 2.90) |
| FIB4 high | 18.42 (15.67, 21.65) | 16.46 (13.65, 19.85) |
| **CV events** | | |
| FIB4 low | 1.00 | 1.00 |
| FIB4 indeterminate | 2.97 (2.82, 3.13) | 1.01 (0.95, 1.07) |
| FIB4 high | 4.73 (4.29, 5.21) | 1.34 (1.21, 1.48) |
| **All-cause mortality** | | |
| FB4 low | 1.00 | 1.00 |
| FIB4 indeterminate | 3.44 (3.29, 3.59) | 0.97 (0.93, 1.02) |
| FIB4 high | 7.25 (6.77, 7.77) | 1.56 (1.45, 1.68) |

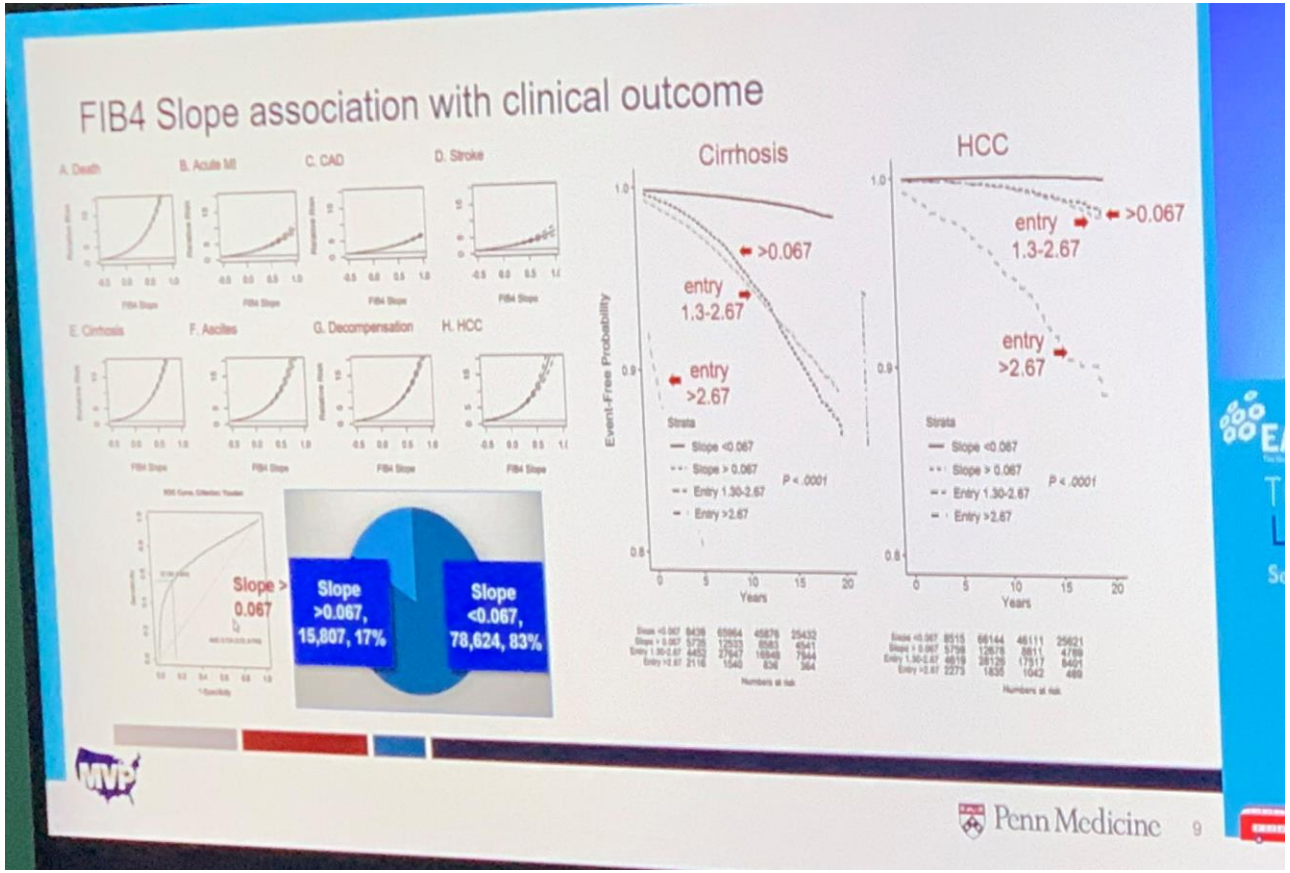
Adjusting for age and sex

- ✓ **CVD events** FIB4 score high vs low
- ✓ **Liver events** FIB 4 low/ intermediate vs high

# NITs and outcome

## serial FIB-4 in the VA cohort

- VA's Million Veteran – longitudinal measures over **20 years** in **61.689 veterans**
- serial FIB-4 scores (≥4 outpatient FIB-4 values) are predictive for decompensation and HCC
- association with genetic variants (GCKR, HSD17B13, and PNPLA3)
- AUC of FIB-4 „slope" to predict *cirrhosis*, *ascites* and *HCC* ranges between 0.75–0.76



# NITs and health care spendings

## A higher Fibrosis-4 (FIB-4) score is associated with higher healthcare costs and hospitalizations in patients with nonalcoholic steatohepatitis (NASH)

- Electronic health records (EHR) with claims database (Veradigm Health Insights)
- Index date (NASH coding between 2016-20220)
- Exploration of hospital admissions and log-transformed costs (pharmacy, hospital inpatient, emergency department) + outpatient services in the 12-month period surrounding index

**Table 1 | Attrition Table**

| Selection Criterion | N | % |
|---|---|---|
| Patients in the Veradigm Integrated Dataset with ≥1 medical claim or EMR with a diagnosis code for NASH between 1/1/2016 and 12/31/2020. Any Dx date was considered a possible index date and evaluated on the criteria below. If multiple index dates meet all criteria, the earliest date was used. | 436,387 | |
| ≥18 years old on the index date | 431,136 | 98.8% |
| ≥6 months of continuous enrollment in closed claims and EMR activity before index date (baseline period) | 50,524 | 11.7% |
| ≥6 months of continuous enrollment in closed claims and EMR activity after index date (follow-up period) | 38,818 | 76.8% |
| Valid AST, ALT, and platelet results in the EMR within 3 months of index date | 9,372 | 24.1% |
| Excluding patients with viral hepatitis, alcoholism, or alcoholic liver disease at any time in patient's available data | 6,743 | 71.9% |

# NITs and health care spendings

## incremental with FIB-4 increase

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**Figure 1 | Hospitalization Rate by FIB-4**

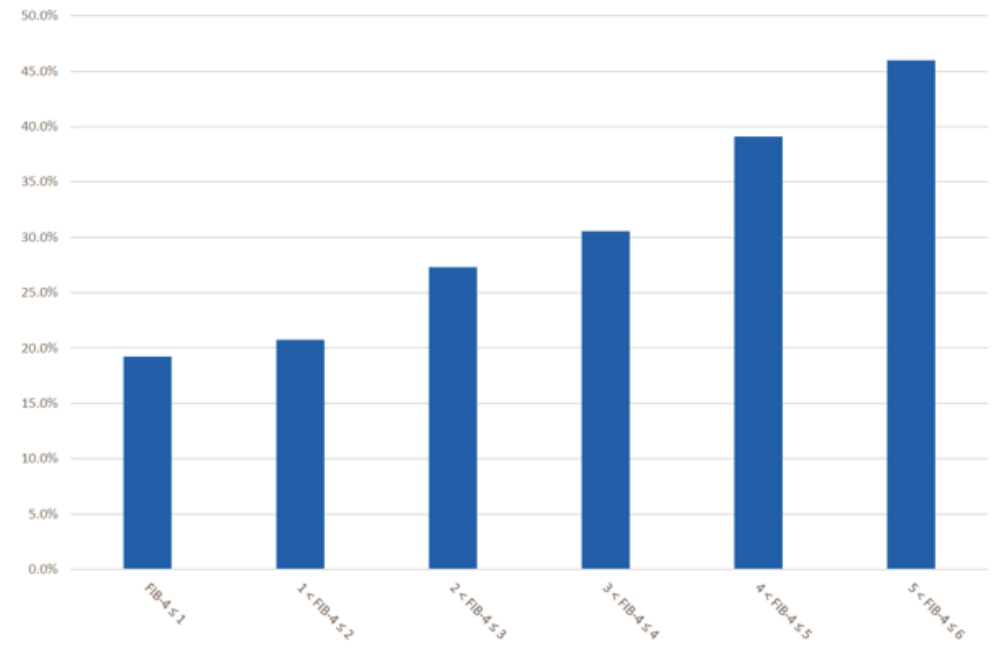
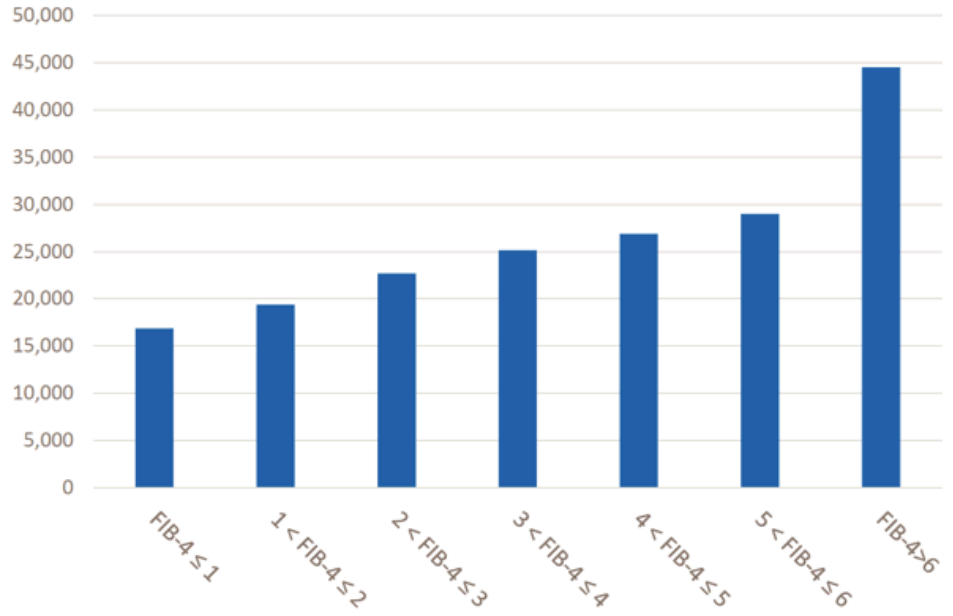



**Figure 2 | Total Cost of Care by FIB-4**




**FIB-4 +1 unit** → 4.2% increase in mean total annual cost (CI 2.2% to 6.3%)
→ odds ratio of 1.12 (CI 1.08 to 1.15) for hospitalisation.

**Higher FIB-4 score across a variety of ranges is associated with increased costs and hospitalizations in the NASH population.**

# Enhanced Liver Fibrosis (ELF)

## predicting liver-outcomes in a population-based cohort



**Background:** Population-based epidemiological survey 2000–2001 (Finland)

Baseline liver disease excluded, age >30y

**Results:** n= 6040 individuals (46% men, age 52.7 ± 15y, BMI 26.9 kg/m$^2$); median follow-up of 13.1 years

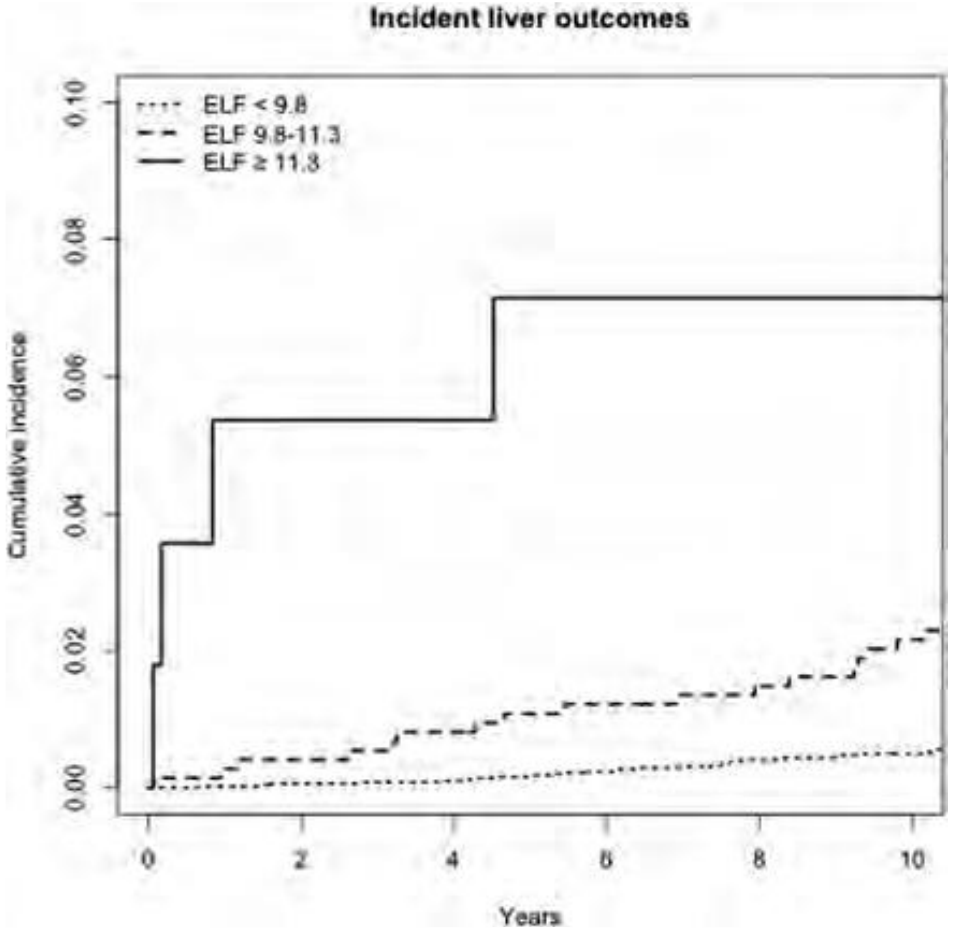
*Severe liver-related outcomes*: 67

(HRs) for liver outcomes

ELF <9.8.: 1

ELF 9.8–11.3: 6.44 (95%CI 3.37–12.29)

ELF ≥11.3: 24.37 (95% CI 8.55–69.50)



# NITs and outcome in special populations

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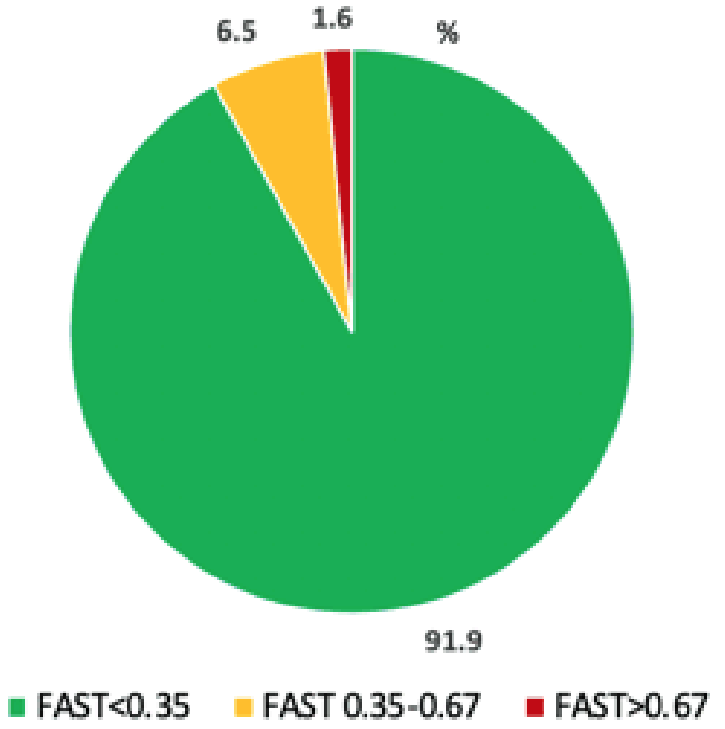
## multicenter analysis in PLWH – **cross sectional**

- 3 prospective cohorts in Canada and Italy in people living with HIV (PLWH)
- Evaluation of the FAST Score (LSM, CAP; AST)
- "at risk" NASH

| Variable (mean or %) | Total (n=1683) |
|---|---|
| Age | 50 ± 10 yrs |
| Male sex | 74% |
| White/Caucasian | 55% |
| Diabetes | 32% |
| BMI | 25 ± 5 Kg/m$^2$ |
| Time since HIV diagnosis | 16 ± 10 yrs |
| CD4 | 688 ± 315 cells/mL |
| ALT | 39 ± 18 IU/L |
| AST | 28 ± 23 IU/L |
| CAP | 237 ± 57 dB/m |
| Liver stiffness | 6.5 ± 5.8 kPa |
| FIB-4 | 1.67 ± 1.41 |

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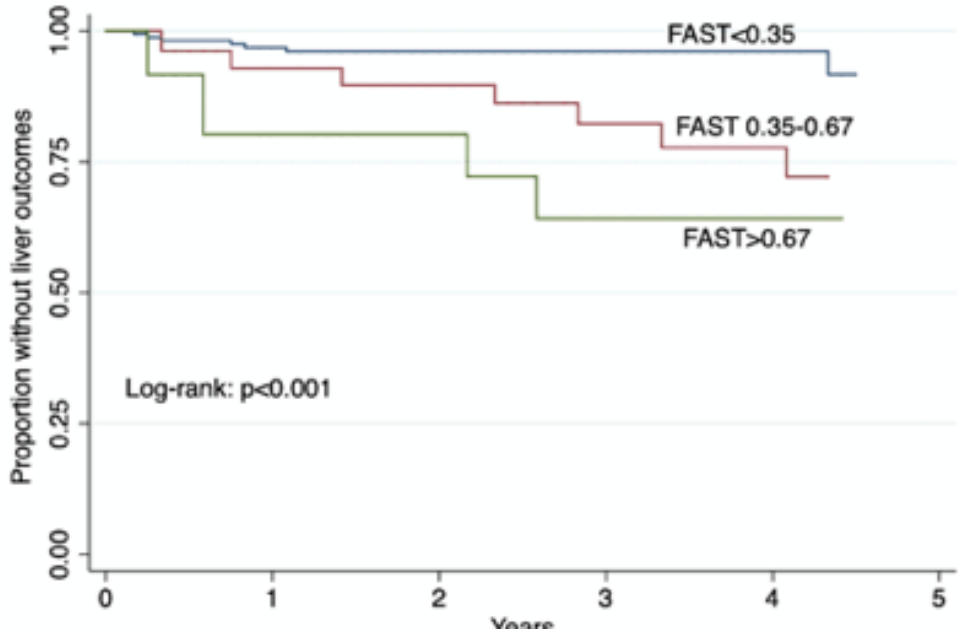
# NITs and outcome in special populations

multicenter analysis in PLWH - **longitudinal**

- Median follow-up 3.5 years
- Incident liver-related outcomes **7%**
- incidence of non-liver outcomes **11.5%**

| Incidence rates (per 100 PY) | FAST<0.35 | FAST>0.35 |
|---|---|---|
| Liver-related outcomes | 1.6 (0.7-3.4) | 7.6 (4.2-13.7) |
| Extra-hepatic outcomes | 4.5 (2.8-7.4) | 7.2 (3.7-13.8) |




Multivariate time-dependent Cox proportional analysis

- FAST >0.35 adjusted **hazard ratio 4.44** (95% CI 1.66 to 11.99) for liver outcomes (adjusted for sex, body mass index, diabetes, HIV duration, protease inhibitor use, and CD4 count below 200).

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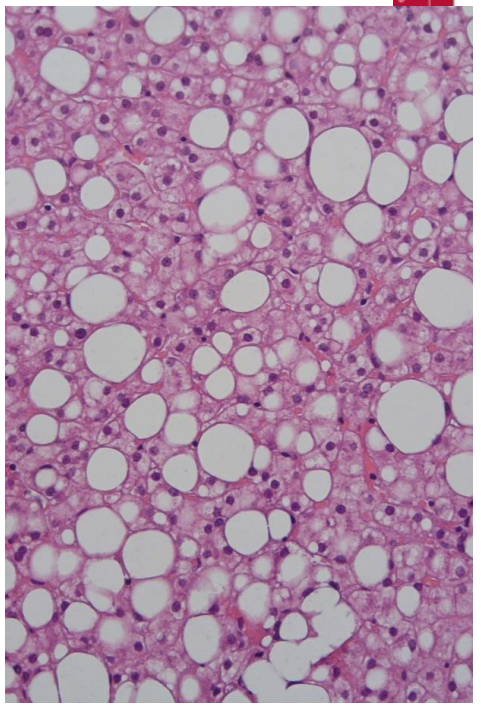


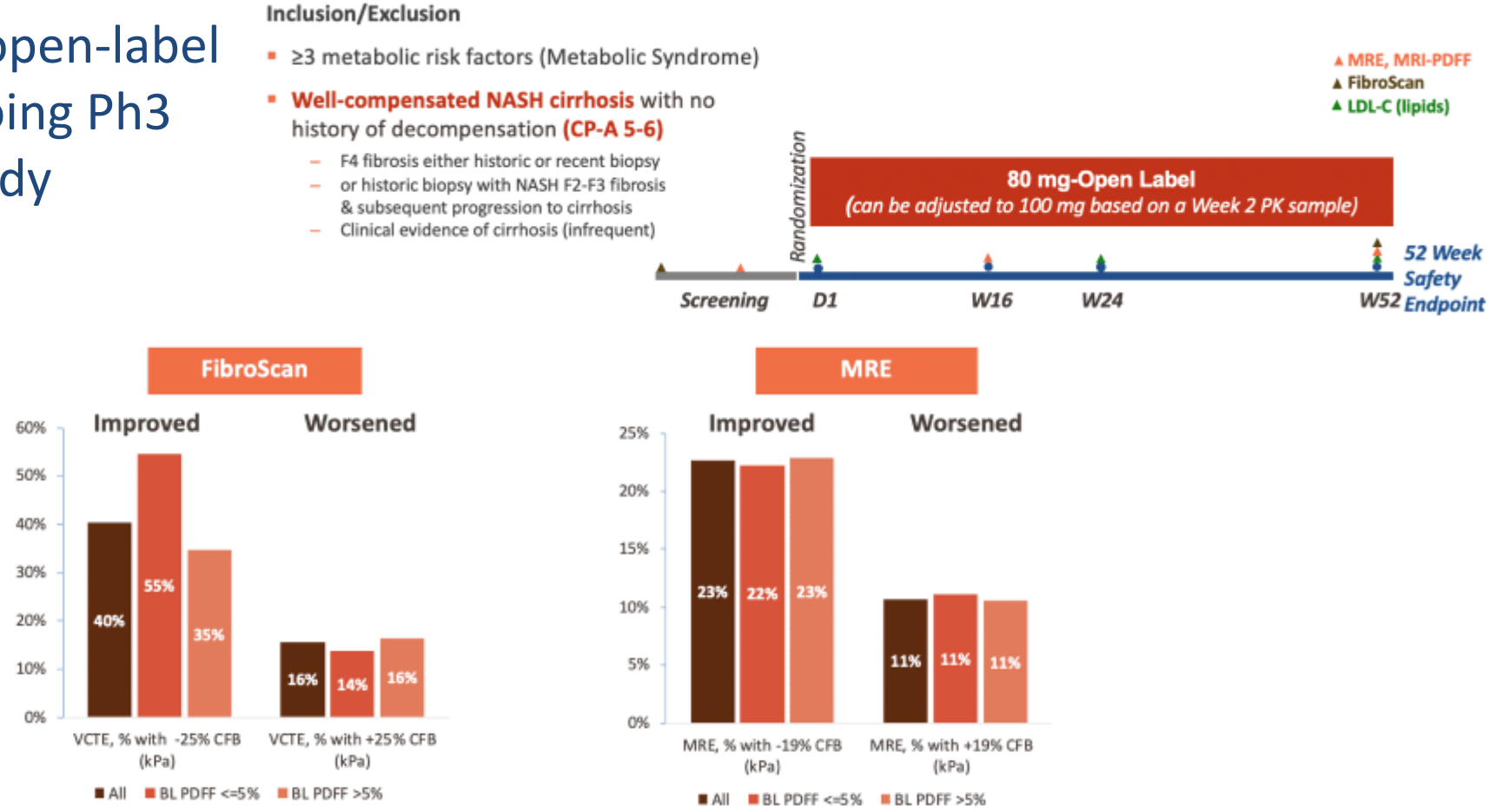
What's new following ILC 2022?

# OUTCOME IN CLINICAL TRIALS

# NIT changes from interventions

## exposure to Resmetirom

- Analysis in the open-label arm of the ongoing Ph3 Resmetirom study program

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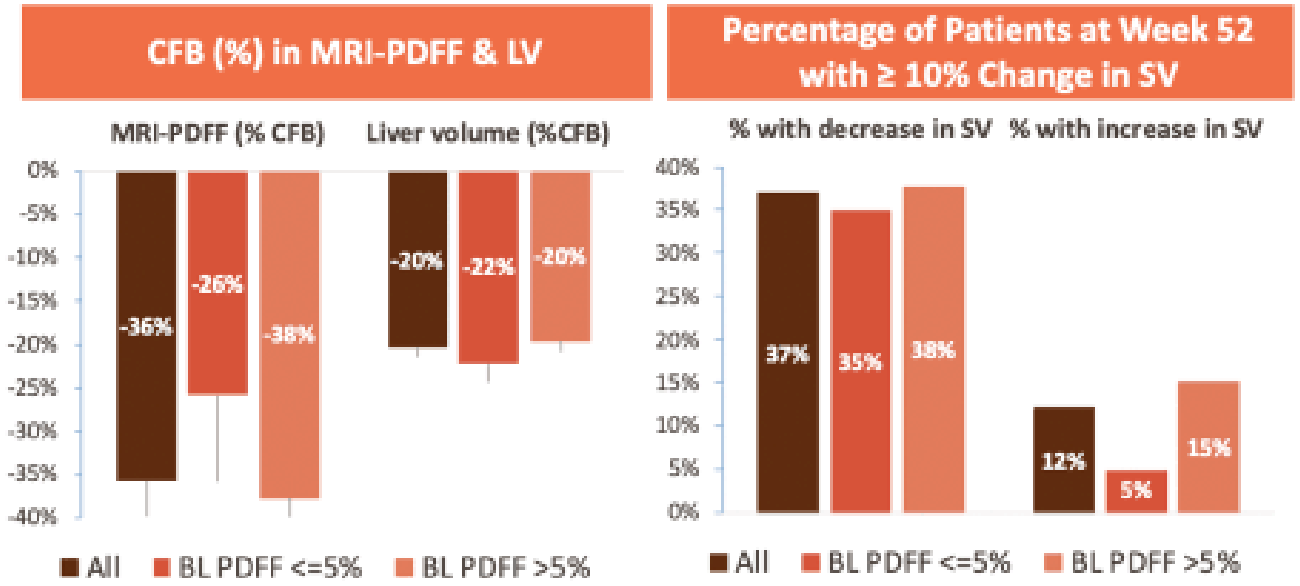
# NITs changes from interventions

## exposure to Resmetirom




- Changes in Liver volume (LV) and spleen volume (SV)
- Even in compensated cirrhosis liver anatomy changes

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# NITs changes from interventions

## exposure to cilofexor / firsocostat / selonsertib

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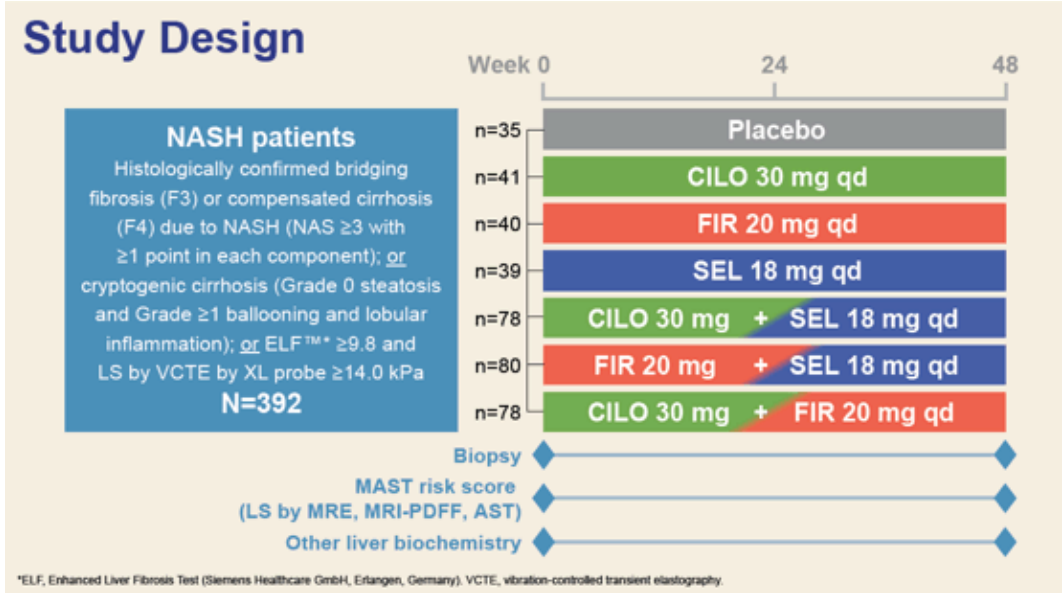
- Ph2b ATLAS study, 48 w
- **Post hoc exploration of changes in the MAST score**

- Assessment of MAST risk score:
  - MAST components measured at BL and Week 48
  - MAST risk score[1] = $\frac{\exp(X)}{1+\exp(X)}$ where $X = -12.17 + 7.07 \times \log(\text{MRE}) + 0.037 \times \text{MRI-PDFF} + 3.55 \times \log(\text{AST})$




### F3 vs F4 Patients

| | | F3: n=39 | F4: n=68 | Overall: N=107 |
|---|---|---|---|---|
| Demographics | Age, y | 58 (53, 64) | 62 (56, 68) | 59 (54, 66) |
| | Female sex at birth | 24 (62) | 48 (71) | 72 (67) |
| | White | 37 (95) | 60 (88) | 97 (91) |
| | BMI, kg/m² | 33.8 (28.9, 39.4) | 34.0 (29.4, 38.7) | 33.8 (29.2, 39.2) |
| | Diabetes | 25 (64) | 54 (79) | 79 (74) |
| ELF | | 9.7 (8.9, 10.2) | 10.2 (9.8, 11.1) | 10.0 (9.5, 10.8) |
| LS by VCTE, kPa | | 12.2 (9.1, 16.6) | 18.2 (14.5, 24.1) | 16.0 (12.0, 21.1) |
| NAS ≥5 | | 34 (87) | 59 (87) | 93 (87) |

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# NITs changes from interventions

exposure to cilofexor / firsocostat / selonsertib

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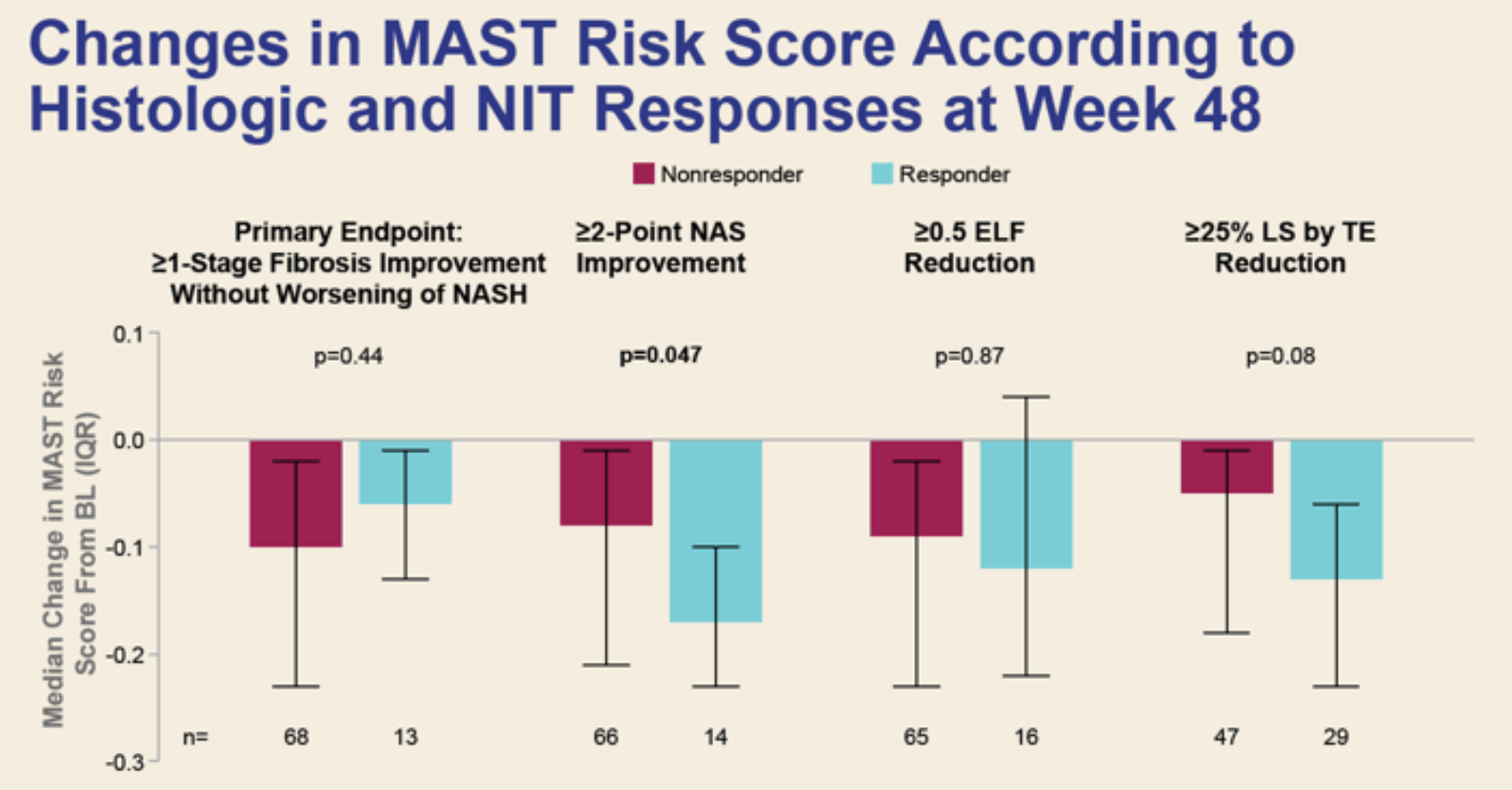


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# Conclusions and points for discussion

## NIT and outcome

- Increasing data on prognostic value of NIT's
- Link to the pathophysiology marks this as important data
- Data from large real-world registries are ready for exploitation
- Stage of transition in patient assessment – NITs will be used to characterize patients – *detached from liver histology*


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