Association between longitudinal biomarkers and major adverse liver outcomes in patients with non-cirrhotic MASLD

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Conclusions

Monitoring non-invasive biomarkers such as FIB-4, AST, and platelet count over time in patients with non-cirrhotic MASLD is important. The latest value of these biomarkers is closely associated with the risk of major adverse liver outcomes. The rate of change may not be important to consider.

Introduction

Non-invasive biomarkers provide prognostic information for future major adverse liver outcomes (MALO) in patients with metabolic dysfunction-associated steatotic liver disease (MASLD), but the predictive value of longitudinal changes of such biomarkers is unclear.

Aim: To assess whether changes in biomarkers could predict incident MALO in non-cirrhotic MASLD.

Study population

1260 patients with MASLD (904, 71.7% by biopsy) from

3 university hospitals between 1974 and 2019 in Sweden

Baseline characteristics

Median age 52 (39-60); 59% male; median BMI 29 (26-32) kg/m^2, MELD 6 (6-8); 25% type 2 diabetes; 66% hypertension; 21% hyperlipidemia

- Biopsy: F0 (24.6%); F1 (41.0%); F2 (23.3%); F3 (11.1%)
- Fibrosis staging by biopsy or VCTE: F0-FI/VCTE<10 kPa (68.3%), F2-F3/VCTE 10-15 kPa (31.7%)
- Median FIB-4: 0.97 (0.69-1.51); Median AST: 0.7 (0.5-1.0) μkat/L; Median platelet count: 241 (198-287) 10^9/L

Repeated measurements:

Baseline (t0)	T1	T2	T3	T4	T5	End of follow up
1 month within 1st liver biopsy	1 year (+/- 6 months) after t0	2 years (+/- 6 months) after t0	5 years (+/- 6 months) after t0	10 years (+/- 1 year) after t0	20 years (+/- 1 year) after t0	last data available

Follow-up was until December 31, 2020. The primary outcome was MALO, defined as a composite endpoint including cirrhosis, decompensated cirrhosis, chronic or unspecified liver failure, transplantation, hepatocellular carcinoma, MELD≥15, or liver-related death from medical charts review or national registers

Results

Figure 1. Trajectories of individual value and population average value of ln(FIB-4), ln(AST) and total platelets count over time prior to development of MALO.

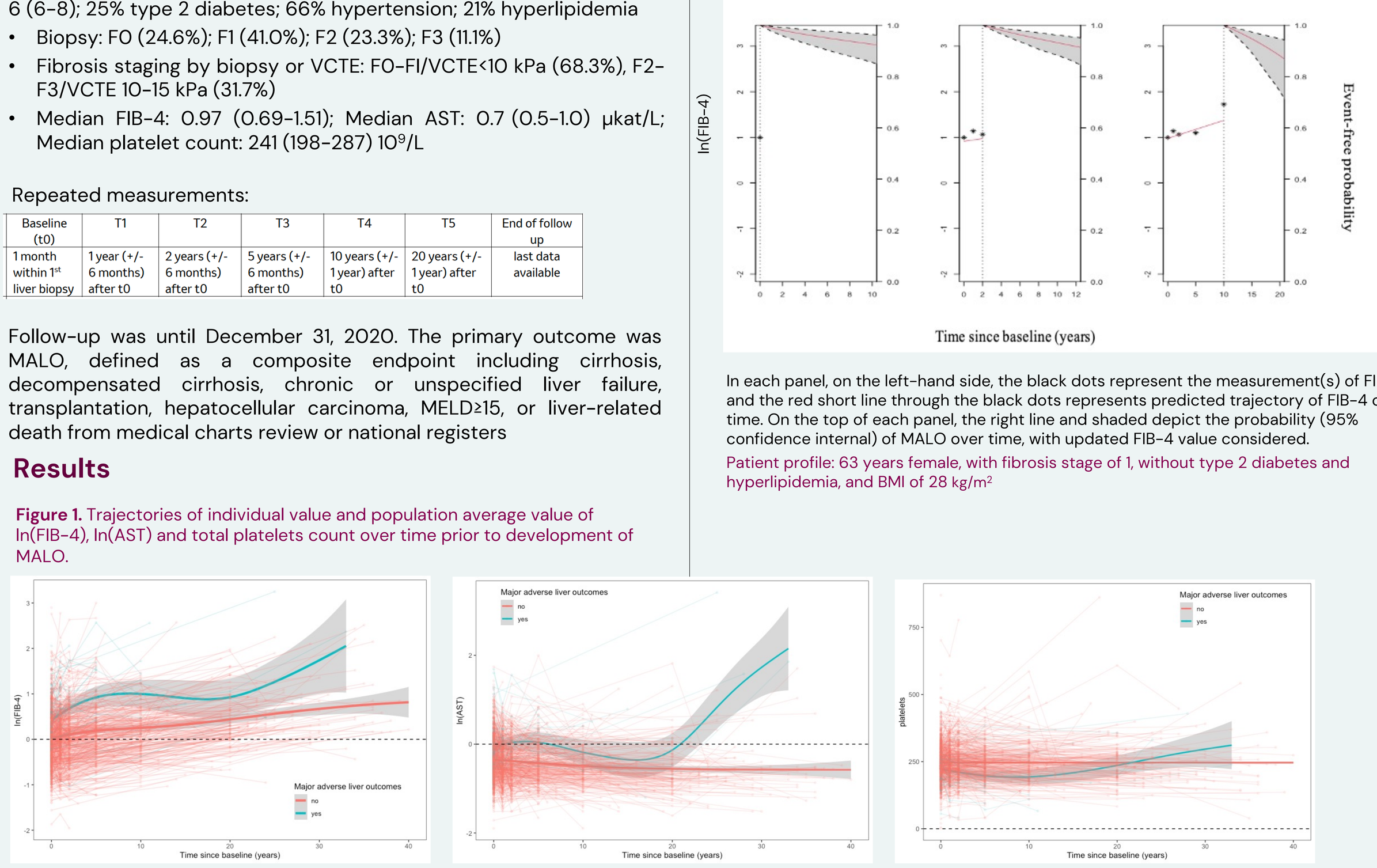

Table 1. The association between longitudinal biomarkers and MALO

Biomarkers	HR (95% CI)#	HR (95% CI)##
ln(FIB-4)		
Longitudinal value of ln(FIB-4)	**2.81 (2.08-3.84)**	**2.60 (1.89-3.50)**
Slope and longitudinal value of ln(FIB-4)		
ln(FIB4)-slope	1.04 (0.96-1.61)	1.04 (0.67-1.61)
ln(FIB4)-value	**2.85 (1.94-4.23)**	**2.77 (1.93-4.00)**
ln(AST), μkat/L		
Longitudinal value of ln(AST)	**3.05 (2.17-4.41)**	**2.77 (1.98-3.94)**
Slope and longitudinal value of ln(AST)		
ln(AST)-slope	0.76 (0.54-1.01)	0.46 (0.17-1.20)
ln(AST)-value	**3.63 (2.38-5.70)**	**3.56 (2.25-5.85)**
Platelets count, 10^9 /L		
Longitudinal value of platelets	**0.93 (0.87-0.97)**	**0.93 (0.90-0.97)**
Slope and longitudinal value of platelets		
Platelets-slope	0.95 (0.88-1.03)	0.91 (0.83-1.02)
Platelets-value	0.95 (0.89-1.02)	0.98 (0.90-1.05)

HR estimated by Joint modelling approach, numbers in bold indicate p<0.05
adjusted for age, sex, BMI, type 2 diabetes, hyperlipidemia
##adjusted for age, sex, BMI, type 2 diabetes, hyperlipidemia, and fibrosis stage

Figure 2. Dynamic prediction given individual's FIB-4 values over time

In each panel, on the left-hand side, the black dots represent the measurement(s) of FIB-4, and the red short line through the black dots represents predicted trajectory of FIB-4 over time. On the top of each panel, the right line and shaded depict the probability (95% confidence internal) of MALO over time, with updated FIB-4 value considered.

Patient profile: 63 years female, with fibrosis stage of 1, without type 2 diabetes and hyperlipidemia, and BMI of 28 kg/m^2

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Declaration: This study was partly funded by a research grant from MSD.

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