

Parallel combination of FIB-4 and Enhanced Liver Fibrosis Test improves prognostication in metabolic dysfunction-associated steatohepatitis

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Background

Metabolic dysfunction-associated steatohepatitis (MASH) is a leading cause of cirrhosis and liver-related mortality. Clinical practice guidance from EASL and other societies recommend sequential measurement by non-invasive tests (NITs) to identify patients most at risk of progressing to liver-related events (LREs). These risk-assessment pathways typically begin with FIB-4 and are followed by either vibration-controlled transient elastography (VCTE) or Enhanced Liver Fibrosis (ELF).^{1,2}

Aim

To determine if parallel measurement of FIB-4 and ELF improves risk stratification in patients with MASH and advanced fibrosis.

Table 1. Demographics and clinical characteristics*

Female, n (%)	1387 (61%)
Type 2 Diabetes, n (%)	1630 (72%)
<50 Years, n (%)	426 (19%)
50-64 Years, n (%)	1352 (59%)
≥65 Years, n (%)	498 (22%)
NASH CRN F3, n (%)	1008 (44%)
NASH CRN F4, n (%)	1265 (56%)
FIB-4 score, median (IQR)	2.20 (1.43, 3.32)
ELF score, median (IQR)	10.32 (9.68, 11.07)

* Based on a total of 2276 study participants.

Table 2. Summary of LREs*

Portal Hypertension-Related Bleeding, n (%)	35 (31%)
Ascites, n (%)	35 (31%)
Hepatic Encephalopathy, n (%)	26 (23%)
MELD ≥15, n (%)	6 (5%)
≥ 2 increase in CPT Score, n (%)	3 (3%)
Transplant, n (%)	1 (1%)
Liver-Related Death, n (%)	2 (2%)
Decompensation Event (Not Specified)	5 (4%)

* Only the first recorded event per patient was included.

Methods

- Population: 2276 patients with MASH and advanced fibrosis (Table 1)
- Dataset: NCT01672866, NCT01672879, NCT024629967, NCT03053050, NCT03053063 (pooled)
- Exclusions: missing ELF or FIB-4 at baseline
- FIB-4 Strata: <1.30, ≥1.30 to <3.48, ≥3.48³
- ELF Strata: <9.00, ≥9.00 to <11.30, ≥11.30 to <12.80, ≥12.80⁴
- ELF testing was performed on ADVIA Centaur XP systems
- Endpoint: Composite endpoint of liver-related events (LREs; Table 2)
- Calculations: event risk (%), events per 1000 years of patient follow-up (LRE/1000 PY), Cox proportional hazard ratio (HR), all with 95% confidence intervals
- Analyses: LRE risk heatmap based on ELF and FIB-4 strata; time-dependent area under the receiver operator characteristic curve [AUC(t)] comparing FIB-4 alone, ELF alone, and FIB-4 + ELF combination; net reclassification improvement

Results

- Median follow-up time of 15.9 months
- 113 study participants had liver-related events during the follow-up period
- A stepwise increase in LREs was observed across FIB-4 and ELF strata, with the highest rates when both markers were highly elevated (Figure 1, Table 3)
- AUC(t) analysis showed improvement of prognostication of FIB-4 + ELF versus either test alone (p<0.05 after 3 months) (Figure 2)
- Compared to FIB-4 alone, the FIB-4 + ELF combination led to a net reclassification improvement (categorical) of 0.44 (95% CI: 0.34, 0.54), including 65 (58%) patients with events correctly up-classified

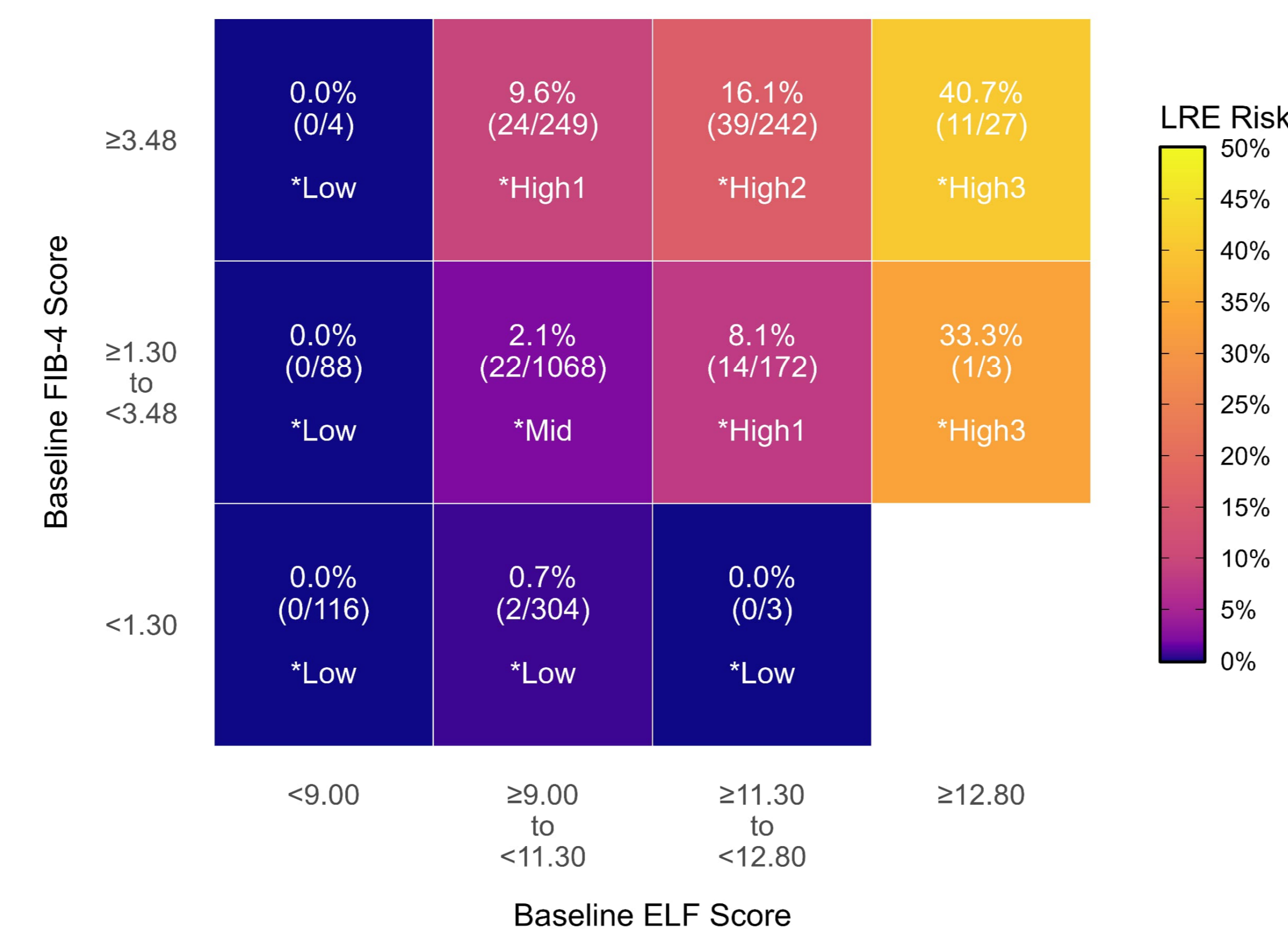


Figure 1. Heatmap of LRE risk based on baseline FIB-4 and ELF scores

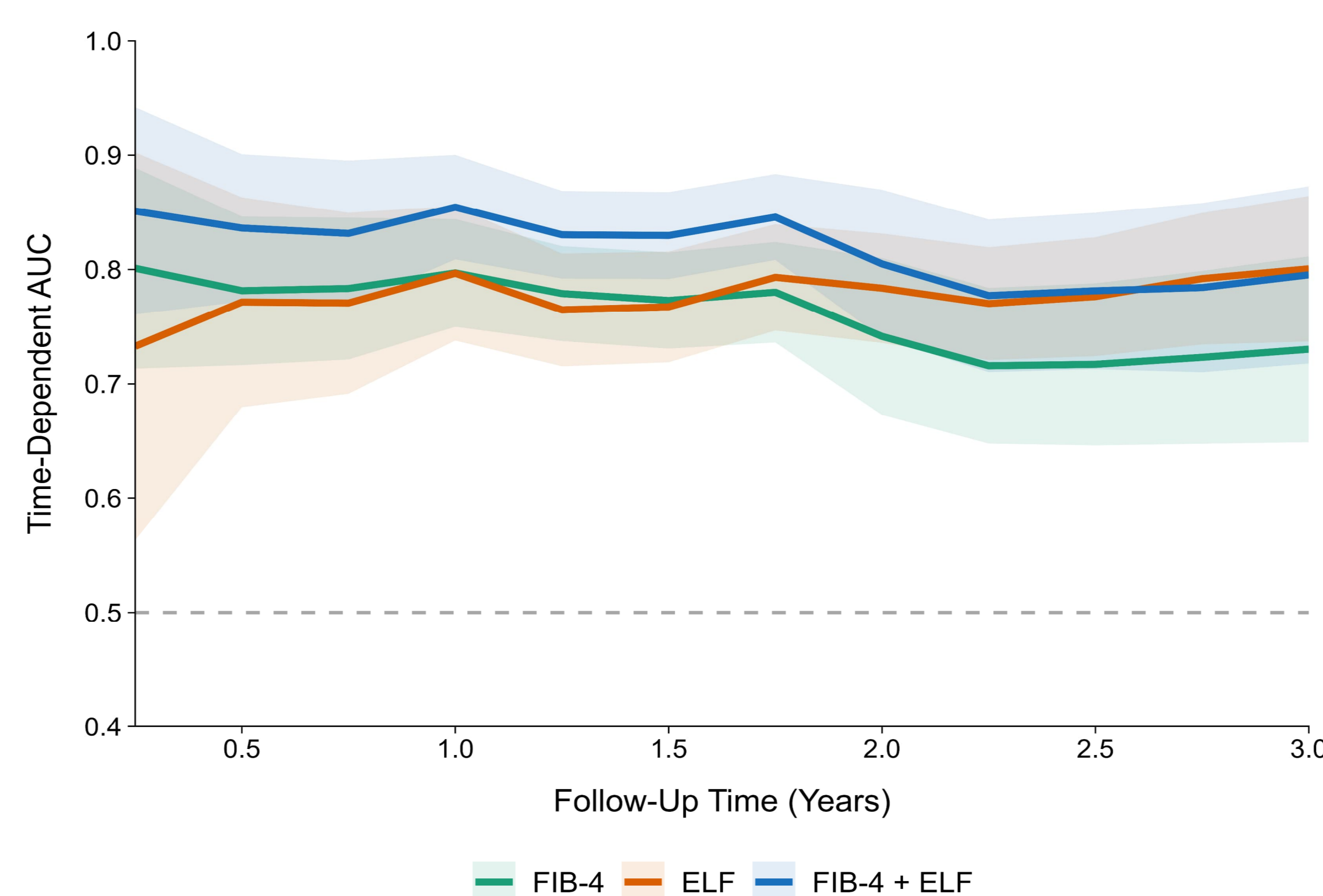


Figure 2. Time-dependent area under the receiver operator characteristic curve [AUC(t)] by parallel measurement of baseline FIB-4 and ELF.

Table 3. LRE incidence stratified by FIB-4 alone, ELF alone, or FIB-4 + ELF combination

Risk Strata	Patients	Events	Event Rate (95% CI)	LRE/1000PY (95% CI)	Cox Proportional HR (95% CI)
Stratification with FIB-4 Alone					
<1.30	423	2	0.5% (0.1%, 1.7%)	3.0 (0.0, 7.6)	---
≥1.30 to <3.48	1331	37	2.8% (2.0%, 3.8%)	19.1 (13.4, 25.3)	6.35 (1.53, 26.34)
≥3.48	522	74	14.2% (11.3%, 17.5%)	105.8 (82.9, 130.1)	35.87 (8.80, 146.16)
Stratification with ELF Alone					
<9.00	208	0	0.0% (0.0%, 1.8%)	0.0 (0.0, 0.0)	---**
≥9.00 to <11.30	1621	48	3.0% (2.2%, 3.9%)	20.2 (14.4, 26.1)	7.16 (0.99, 51.90)
≥11.30 to <12.80	417	53	12.7% (9.7%, 16.3%)	96.9 (71.3, 124.4)	35.99 (4.97, 260.59)
≥12.80	30	12	40.0% (22.7%, 59.4%)	407.7 (203.9, 645.6)	170.77 (22.08, 1320.9)
Stratification with FIB-4 + ELF					
Low*	515	2	0.4% (0.0%, 1.4%)	2.5 (0.0, 6.2)	---
Mid	1068	22	2.1% (1.3%, 3.1%)	14.2 (8.4, 20.6)	5.86 (1.38, 24.91)
High1	421	38	9.0% (6.5%, 12.2%)	63.4 (43.4, 85.1)	26.55 (6.40, 110.07)
High2	242	39	16.1% (11.7%, 21.4%)	127.4 (88.2, 169.8)	54.18 (13.07, 224.51)
High3	30	12	40.0% (22.7%, 59.4%)	407.7 (203.9, 645.6)	194.35 (43.27, 872.84)
Overall	2276	113	5.0% (4.1%, 5.9%)	34.3 (28.2, 40.6)	---

* FIB-4 + ELF combination strata: Low (FIB-4 <1.30 and/or ELF <9.00), Mid (FIB-4 ≥1.30 to <3.48 & ELF ≥9.00 to <11.30), High1 (FIB-4 ≥1.30 to <3.48 & ELF ≥11.30 to <12.80 OR FIB-4 ≥3.48 & ELF ≥9.00 to <11.30), High2 (FIB-4 ≥3.48 & ELF ≥11.30 to <12.80), High3 (FIB-4 ≥1.30 & ELF ≥12.80).

** For the Cox analysis, ELF <9.02 was used as the reference group because there were no events <9.00.

Conclusions

The parallel measurement of FIB-4 and ELF improves prognostic performance over that of the individual tests and offers a pragmatic option to facilitate prognostic clinical decision making in patients with MASLD/MASH, especially in settings where imaging elastography is not readily available.

References

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