1-year change in Enhanced Liver Fibrosis (ELF) predicts liver-related clinical events in patients with metabolic dysfunction-associated steatohepatitis

Matthew F. W. Gee,[1,2] Edward B. De Vol,[2] William M. Rosenberg,[3] Jordan J. Feld,[1,4] Keyur Patel,[1,4] and Arun J. Sanyal[5]

[1]Institute of Medical Science, Temerty Faculty of Medicine, University of Toronto, Toronto, ON, Canada; [2]Siemens Healthcare Diagnostics Inc., 511 Benedict Ave, Tarrytown, NY, United States; [3]Institute for Liver and Digestive Health, University College London, London, United Kingdom; [4]Division of Gastroenterology, University Health Network, Toronto General Hospital, Toronto, ON, Canada; [5]Virginia Commonwealth University School of Medicine, Richmond, VA, United States

Background

The U.S. Food and Drug Administration recently called for more evidence to enable the use of non-invasive tests as alternatives to liver biopsy as a reasonably likely surrogate endpoint (RLSE) in MASH clinical trials.[1] Although histological endpoints have been historically used in MASH clinical trials, due to safety, accuracy, and cost concerns associated with biopsy, an alternative non-invasive option is desirable.[2]

Aim

To determine if serial changes in ELF scores can differentiate the risk of liver-related events (LREs).

Methods

- Population: 2071 patients with MASH and advanced fibrosis (demographics in Table 1)
- Dataset: Pool of NCT01672866, NCT01672879, NCT024629967, NCT03053050, NCT03053063
- Exclusions: missing ELF or histology at baseline or 1 years
- ELF Strata: Baseline (Low: <9.80, Mid: ≥9.80 to <11.30, High: ≥11.30); 1-year change by category (Low, Mid, High) or magnitude (↓ ≥0.50 units, stable, ↑ ≥0.50 units)
- NASH CRN strata: Baseline F3 or F4; 1 year <F3, F3, F4
- ELF testing was performed on ADVIA Centaur XP systems
- Endpoint: Composite endpoint of clinical manifestations of decompensation (Table 2), measured concurrently, excluding events occurring within 1 year in patients without recorded histology
- Calculations: event risk (%), interval likelihood ratio (iLR) and events per 1000 years of patient follow-up (LRE/1000 PY), all with 95% confidence intervals

Table 1. Baseline demographics and clinical characteristics*

Female, n (%)	1260 (60.8%)
Type 2 Diabetes, n (%)	1393 (67.3%)
<50 Years, n (%)	375 (18.1%)
50-64 Years, n (%)	1239 (59.8%)
≥65 Years, n (%)	457 (22.1%)
NASH CRN Stage F3, n (%)	933 (45.1%)
NASH CRN Stage F4, n (%)	1138 (54.9%)
FIB-4 score, median (IQR)	2.19 (1.43, 3.30)
ELF score, median (IQR)	10.30 (9.67, 11.04)

* A total of 2071 study participants included in this analysis.

Table 2. Summary of LREs*

Portal Hypertension-Related Bleeding, n (%)	32 (36.4%)
Ascites, n (%)	25 (28.4%)
Hepatic Encephalopathy, n (%)	17 (19.3%)
MELD ≥15, n (%)	5 (5.7%)
≥ 2 increase in CPT Score, n (%)	3 (3.4%)
Transplant, n (%)	1 (1.1%)
Liver-Related Death, n (%)	1 (1.1%)
Decompensation Event (Not Specified)	4 (4.5%)

* Only the first recorded event per patient was used in the analysis.

Results

- Median follow-up time of 16.4 months
- 88 study participants had liver-related events during the follow-up period (4.2% overall event risk)
- An increased risk of LREs was associated with a smaller incremental change in ELF at 1 year in patients starting with a higher baseline ELF score (Figure 1)
- After baseline adjustment, groups with worsening ELF were associated with a higher incidence of LREs while groups with improving ELF were associated with fewer LREs (Table 3, Figure 2)
- The event risk for the highest histological group (F4 at baseline & 1 year) was lower than the highest ELF strata for categorical and magnitude change

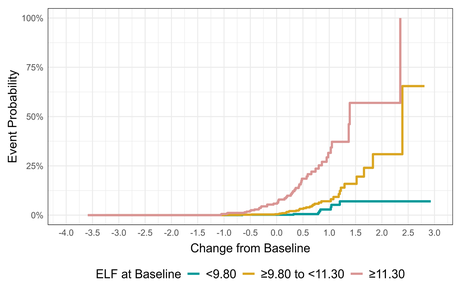

Figure 1. Probability of LREs by change of ELF from baseline to 1 year stratified by baseline value.

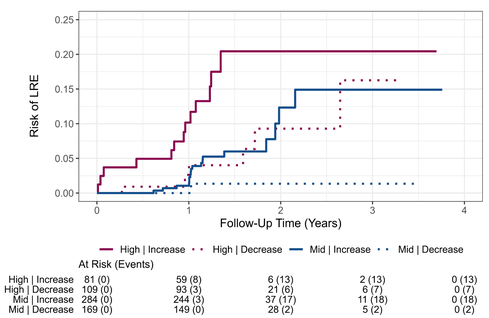

Figure 2. Cumulative incidence of LREs based on a 1-year increase or decrease in ELF score adjusted for baseline ELF category. Purple lines: patients categorized as High ELF (≥11.30) at baseline, Blue lines: patients categorized as Mid ELF (≥9.80 to <11.30) at baseline, Solid lines: patients with an increase of ELF by ≥0.5 units at 1 year, Dashed lines: patients with a decrease of ELF by ≥0.5 units at 1 year.

Table 3. LRE incidence stratified by ELF and NASH CRN at baseline and 1 year

Baseline	1 Year	Patients (N)	LREs (N)	Risk of LREs (95% CI)	iLR (95% CI)	LRE / 1000 PY (95% CI)
ELF Score (categorical change)						
	High	282	41	14.5% (10.6%, 19.2%)	3.83 (2.98, 4.94)	112.5 (79.6, 148.2)
High	Mid	105	5	4.8% (1.6%, 10.8%)	1.13 (0.47, 2.70)	29.2 (5.8, 58.4)
	Low	4	0	0.0% (0.0%, 60.2%)	0.00	0.0
	High	180	16	8.9% (5.2%, 14.0%)	2.20 (1.38, 3.51)	62.0 (34.9, 93.1)
Mid	Mid	742	17	2.3% (1.3%, 3.6%)	0.53 (0.34, 0.81)	15.3 (8.1, 23.4)
	Low	149	1	0.7% (0.0%, 3.7%)	0.15 (0.02, 1.08)	4.2 (0.0, 12.7)
	High	4	0	0.0% (0.0%, 60.2%)	0.00	0.0
Low	Mid	194	7	3.6% (1.5%, 7.3%)	0.84 (0.41, 1.74)	24.2 (6.9, 44.9)
	Low	411	1	0.2% (0.0%, 1.3%)	0.05 (0.01, 0.39)	1.4 (0.0, 4.3)
ELF Score (magnitude change)						
	Increase	81	13	16.0% (8.8%, 25.9%)	4.31 (2.48, 7.49)	124.0 (57.2, 200.2)
High	Stable	201	26	12.9% (8.6%, 18.4%)	3.35 (2.35, 4.76)	98.8 (64.6, 136.7)
	Decrease	109	7	6.4% (2.6%, 12.8%)	1.55 (0.74, 3.23)	40.2 (11.5, 74.6)
	Increase	284	18	6.3% (3.8%, 9.8%)	1.52 (0.99, 2.34)	42.3 (23.5, 63.4)
Mid	Stable	618	14	2.3% (1.2%, 3.8%)	0.52 (0.32, 0.85)	15.4 (7.7, 24.1)
	Decrease	169	2	1.2% (0.1%, 4.2%)	0.27 (0.07, 1.07)	7.5 (0.0, 18.7)
	Increase	225	6	2.7% (1.0%, 5.7%)	0.62 (0.28, 1.35)	17.4 (5.8, 32.0)
Low	Stable	317	1	0.3% (0.0%, 1.7%)	0.07 (0.01, 0.50)	1.9 (0.0, 5.7)
	Decrease	67	1	1.5% (0.0%, 8.0%)	0.34 (0.05, 2.43)	8.8 (0.0, 26.3)
NASH CRN						
	F4	965	76	7.9% (6.3%, 9.8%)	1.93 (1.75, 2.12)	52.1 (40.5, 64.5)
F4	F3	165	6	3.6% (1.3%, 7.7%)	0.85 (0.39, 1.87)	25.6 (8.5, 46.9)
	<F3	8	0	0.0% (0.0%, 36.9%)	0.00	0.0
	F4	148	2	1.4% (0.2%, 4.8%)	0.31 (0.08, 1.23)	14.9 (0.0, 37.2)
F3	F3	643	4	0.6% (0.2%, 1.6%)	0.14 (0.05, 0.37)	3.8 (0.9, 7.6)
	<F3	142	0	0.0% (0.0%, 2.6%)	0.00	0.0

Low: <9.80, Mid: ≥9.80 to <11.30, High: ≥11.30; Increase: ≥ +0.5-unit change; Stable: > -0.5 to < +0.5-unit change; Decrease: ≤ -0.5-unit change.

Conclusions

Risk strata defined by serial changes in ELF are associated with differences in clinical outcome risk. Serial measurement of ELF may be useful to identify patients most likely to show MASH improvement or worsening and holds promise as a reasonably likely surrogate endpoint to potentially replace histology in clinical trials.

References

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