Moving ELF closer to a Reasonably Likely Surrogate Endpoint

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Disclosures and disclaimers

Matt Gee is an employee of Siemens Healthineers

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The information presented herein reflects a potential context of use (COU)
for monitoring in clinical trials and drug development.
In the U.S., the ELF Test is currently limited to prognostic use for clinical practice.

U.S. Intended Use:

The ELF Test is indicated as a prognostic marker in conjunction with other laboratory findings and clinical assessments in patients with advanced fibrosis (F3 or F4) due to non-alcoholic steatohepatitis (NASH) to assess the likelihood of progression to cirrhosis and liver-related clinical events.

Outside U.S. Intended Use:

The ELF Test is indicated, in conjunction with other laboratory findings and clinical assessments, for the assessment of severity of liver fibrosis in patients with signs, symptoms, or risk factors of chronic liver disease. The ELF Test may be used diagnostically for fibrosis staging or prognostically to assess the likelihood of progression to cirrhosis and liver-related clinical events.

The elephant in the room…

Additional disclosure: I am Canadian

Trump imposes tariffs on Canada, Mexico and China

It's the first official action of the president's second-term trade war.

Canada warns Trump on tariffs: Retaliation is coming April 2

By Max Saltman, Betsy Klein and David Goldman, CNN

5 minute read · Updated 9:33 PM EDT, Sat March 29, 2025

Ontario premier threatens to 'shut off electricity completely' for US if trade war escalates

By Max Saltman, CNN

2 minute read · Updated 12:47 PM EDT, Tue March 11, 2025

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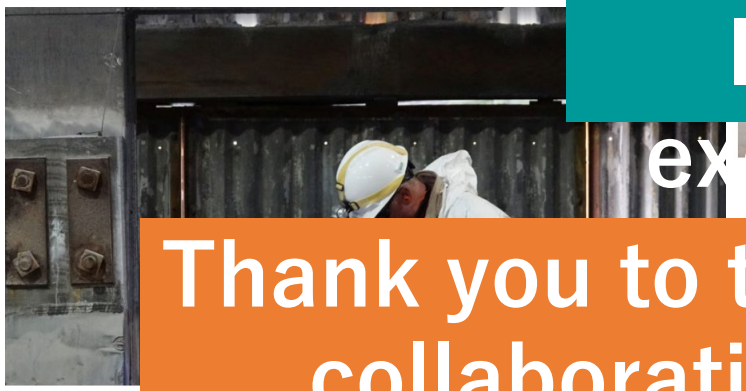
Due to the tariffs on Canada…

I am legally required to exceed my allotted time by



WASH GTON A FORUM

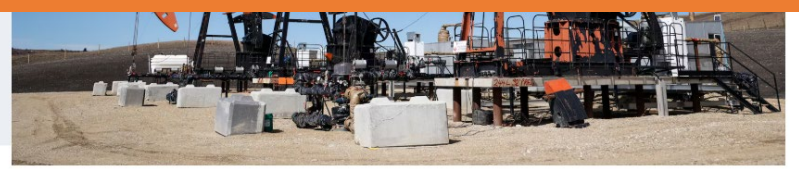
PUBLISHED MARCH 26, 2025

UPDATED MARCH 27, 2025

Thank you to the Liver Forum, where international collaboration and mutual respect is valued.

After brief trade truce, U.S. slaps levy on Canadian aluminum

Economy Aug 14, 2020 6:53 PM EDT



Is ELF a potential reasonably likely surrogate endpoint?

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Questions raised about ELF as RLSE

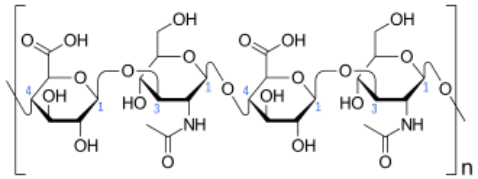
1. Validity of ELF performance
2. ELF performance in diabetics
3. ELF versus individual markers
4. Association of ELF change with change in LRE risk
5. Combination of ELF and VCTE

LREs: liver-related clinical events (decompensation events, [indication for] transplant, liver-related death

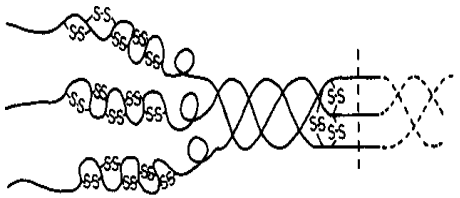
Overview of Enhanced Liver Fibrosis (ELF) Test

ELF Test:

- Serum-based non-invasive test (NIT) run on Atellica IM and Atellica CI Analyzers*
- Multianalyte assay with algorithmic analysis (MAAA)
- Measures direct markers of fibrosis: HA, PIIINP and TIMP-1
- Combines quantitative measurements into a unitless ELF score



Hyaluronic acid (HA)



Procollagen III amino terminal peptide (PIIINP)

$$\text{ELF score} = 2.278 + 0.851 \times \ln(C_{HA}) + 0.751 \times \ln(C_{PIIINP}) + 0.394 \times \ln(C_{TIMP\text{-}1})$$

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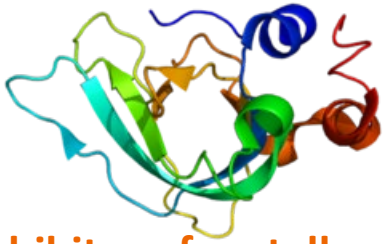
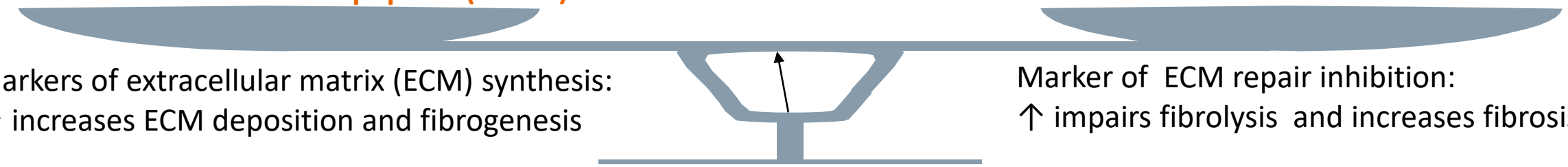


Tissue inhibitor of metalloproteinase-1 (TIMP-1)



Markers of extracellular matrix (ECM) synthesis:
↑ increases ECM deposition and fibrogenesis

Marker of ECM repair inhibition:
↑ impairs fibrolysis and increases fibrosis

Arpino V, Brock M, Gill SE. The role of TIMPs in regulation of extracellular matrix proteolysis. Matrix Biol 2015;44-46:247-54.
Rosenberg WM, Voelker M, Thiel R, et al. Serum markers detect the presence of liver fibrosis: a cohort study. Gastroenterology 2004;127:1704-13.

- Also run on legacy ADVIA Centaur XP/XPT/CP systems; ** ELF run on ADVIA Centaur CP uses a different equation

ELF as a prognostic marker (in MASH)

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Baseline ELF outperforms histology to predict disease progression

Likelihood ratio (95% CI) for prognostication of LREs or histological events by ELF score and NASH CRN

Baseline Measurement (ELF Score or NASH CRN)	Prediction of Progression to LREs Within ~18 Months (N = 2304)	Prediction of Progression to Cirrhosis (NASH CRN F4) at 1 Year (N = 1072)
≥12.80	12.5 (6.1, 25.3)	4.2 (2.9, 6.0)
≥11.30 to <12.80	2.8 (2.3, 3.5)	
≥9.80 to <11.30	0.7 (0.5, 0.9)	1.1 (1.0, 1.3)
≥9.00 to <9.80	0.3 (0.2, 0.65)	0.5 (0.4, 0.7)
≥8.30 to <9.00	0.0	
<8.30		0.0
NASH CRN F4	1.7 (1.6, 1.8)	
NASH CRN F3	0.2 (0.1, 0.4)	---

Patients with F3-F4 MASH

Modified from: Sanyal A, Fonstad R, Brown C, Gee M. Hepatology. 2024;80(S1):S658. **Presented at AASLD (The Liver Meeting) 2024**

ELF as a prognostic marker (independent validation)

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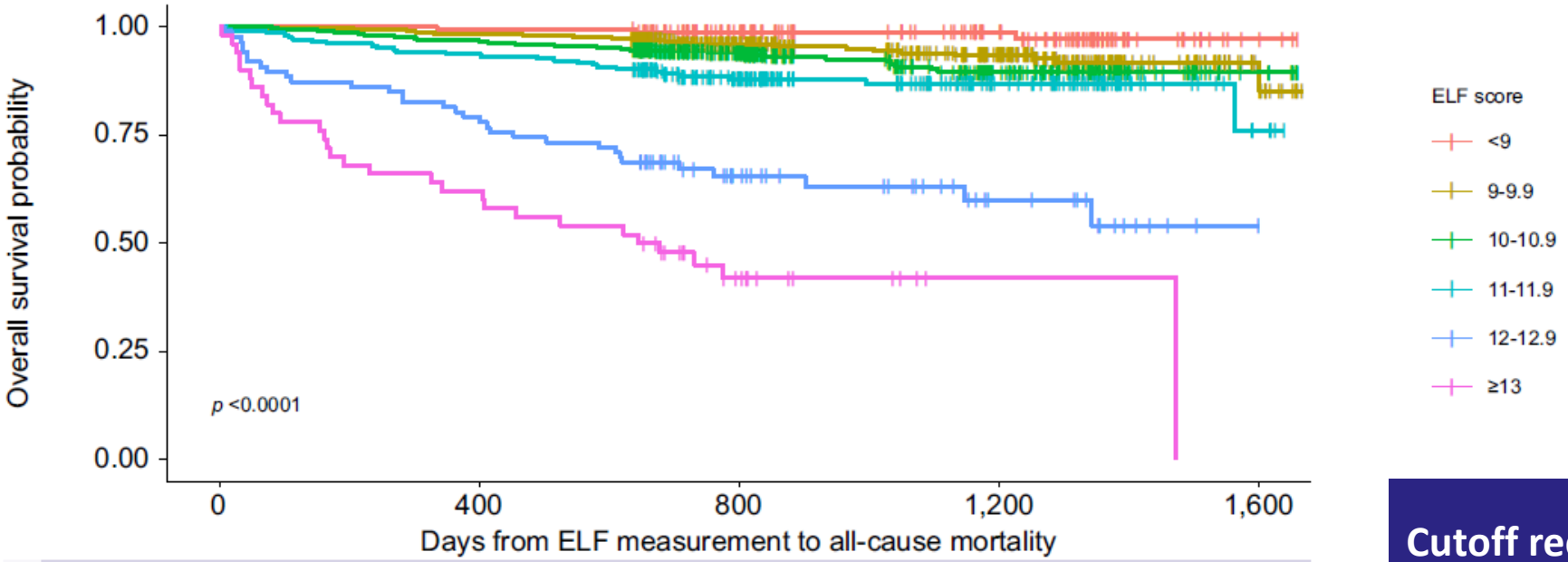
Independent validation of ELF prognostic cutoffs (1327 individuals recruited using primary care pathways)



ELF score	N° at risk					
<9	155	154	109	65	4	
9-9.9	428	420	275	150	14	
10-10.9	405	392	246	109	6	
11-11.9	203	190	124	56	4	
12-12.9	86	68	35	14	1	
≥13	50	31	12	1	0	

Cutoff recommendations:
<9.00: Minimal risk of events
≥9.80: Elevated risk of events
≥11.30: High risk of events
≥12.80: Urgent care warranted

Pearson M, Nobes J, Macpherson I, et al. JHEP Rep. 2024;6(6):101062.

Precision of the ELF Test on the Atellica IM Analyzer

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Single-site precision

Sample	Mean ELF Score	Repeatability SD[a] (ELF Score)	Repeatability CV[b] (%)	Within-Laboratory Precision SD (ELF Score)	Within-Laboratory Precision CV (%)
1	9.54	0.02	0.2	0.04	0.4
2	7.67	0.04	0.5	0.08	1.0
3	7.40	0.04	0.6	0.10	1.3
4	11.59	0.04	0.4	0.05	0.4
5	12.53	0.05	0.4	0.06	0.5
6	13.68	0.03	0.2	0.05	0.4
7	7.91	0.02	0.3	0.04	0.5

Multi-site precision

Sample (N = 90)	Mean ELF Score	Repeatability SD[a] (ELF Score)	Repeatability CV[b] (%)	Between-Run SD (ELF Score)	Between-Run CV (%)	Between-Day SD (ELF Score)	Between-Day CV (%)	Between-Site SD (ELF Score)	Between-Site CV (%)	Reproducibility SD (ELF Score)	Reproducibility CV (%)
Serum 1	7.43	0.05	0.6	0.05	0.7	0.00	0.0	0.03	0.4	0.07	1.0
Serum 2	11.54	0.04	0.4	0.06	0.5	0.00	0.0	0.09	0.8	0.12	1.0
Serum 3	12.62	0.05	0.4	0.04	0.3	0.00	0.0	0.10	0.8	0.12	1.0
Serum 4	9.87	0.05	0.5	0.02	0.2	0.02	0.2	0.06	0.6	0.08	0.8
Serum 5	12.46	0.05	0.4	0.07	0.5	0.00	0.0	0.09	0.8	0.13	1.0
Serum 6	13.63	0.04	0.3	0.06	0.4	0.00	0.0	0.07	0.5	0.10	0.7
Serum 7	9.34	0.05	0.6	0.04	0.5	0.00	0.0	0.04	0.4	0.08	0.8
Serum 8	7.91	0.06	0.7	0.01	0.2	0.02	0.2	0.06	0.8	0.08	1.1

[a] Standard deviation.
[b] Coefficient of variation.

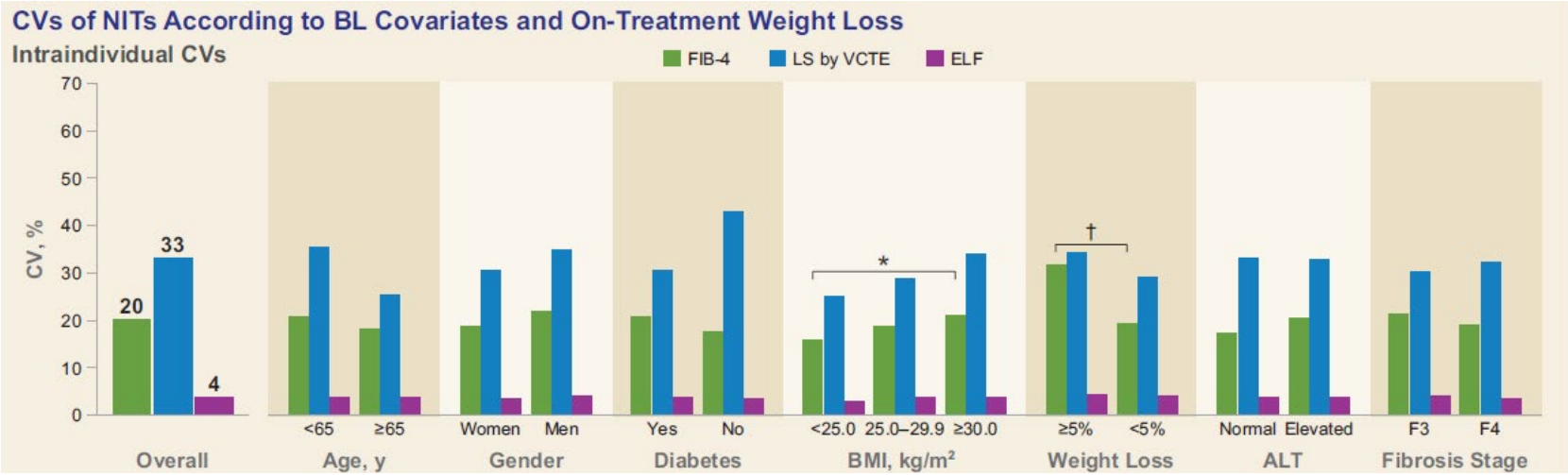
Assigned bias threshold: 0.3 units

A change of ELF >0.3 units is likely significant

Palladino A, Gee M, Shalhoub V, Kiaei D. Clin Chim Acta. 2023:548:117461.
Atellica IM ELF Instructions for Use. 11208159_EN Rev. 02, 2022-10

ELF is the among the most precise of NITs

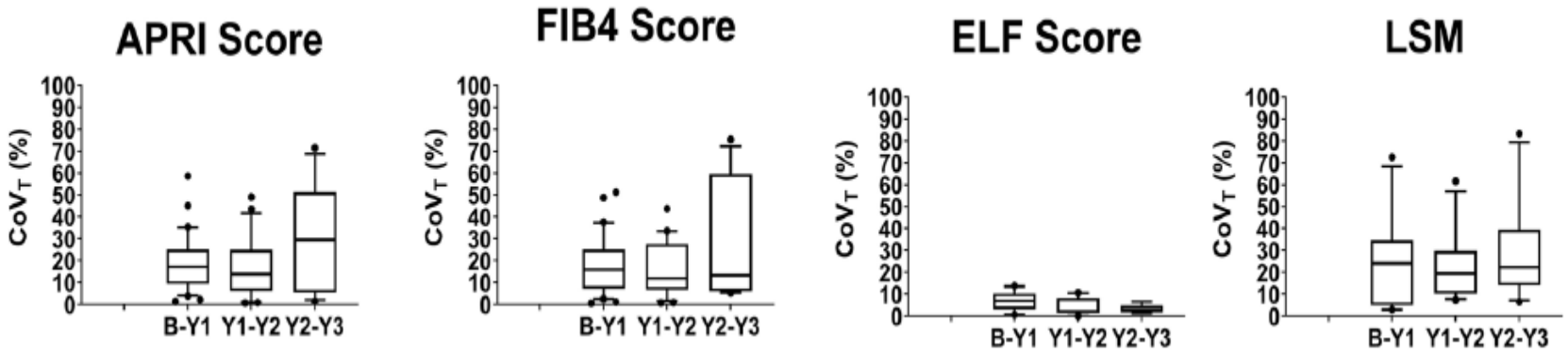
Patients with MASH



ELF precision: 3.8% CV

"In NASH patients with stable, advanced fibrosis…ELF may have greater precision for disease monitoring in NASH."

Patients with compensated cirrhosis



ELF precision: 4.0% CV

"Among the clinical measures, ELF was most consistent"

Anstee Q et al. J Hepatol. 2021;75(S2):S575-S576. **Presented at EASL (ILC) 2021**
Bradley CR, Cox EF, Palaniyappan N, et al. Eur Radiol Exp. 2022;6(1):52.
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Is ELF a potential reasonably likely surrogate endpoint?

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Questions raised about ELF as RLSE

✓1. Validity of ELF performance

2. ELF performance in diabetics

3. ELF versus individual markers

4. Association of ELF change with change in LRE risk

5. Combination of ELF and VCTE

ELF performance in diabetics

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Prognostic performance is highly comparable in patients with/without diabetes

Baseline ELF Score	Diabetes Status	N	LRE	Risk of LRE
≥11.30	Diabetes	288	36	12.5% (8.9%, 16.9%)
	No Diabetes	113	14	12.4% (6.9%, 19.9%)
≥9.80 to <11.30	Diabetes	825	23	2.8% (9.4%, 16.1%)
	No Diabetes	285	7	2.5% (1.8%, 4.2%)
<9.80	Diabetes	434	2	0.5% (1.0%, 5.0%)
	No Diabetes	199	2	1.0% (1.8%, 3.8%)

2144 patients with F3-F4 MASH and known diabetes status

Manuscript in preparation.

Influence of glycemic control on ELF

What is the relationship of HbA1c and ELF performance?

No literature evidence. HbA1c is not included in internal datasets.

Does glycemic control influence HA?

Nagy N, et al. (Matrix Biol. 2018;80:46–58)

We find no relationship between serum HA and glycemic control, insulin production, or BMI.

There is no evidence to suggest that improvement in glycemic control or diabetes status will directly influence the ELF score.

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HA often changes in tandem with PIIINP/TIMP-1

Serial changes in ELF and individual analytes – 1926 patients with MASH and advanced fibrosis

LREs	Timepoint	HA (Mean)	PIIINP (Mean)	TIMP-1 (Mean)	ELF (Mean)
Yes	Baseline	393.76	14.23	371.27	11.29
	1 Year	566.40	16.01	408.71	11.65
	Difference	44%	12%	10%	0.35
No	Baseline	157.07	12.74	302.27	10.31
	1 Year	185.36	12.44	299.15	10.40
	Difference	18%	-2%	-1%	0.09

Larger changes in ELF and individual markers in patients who develop LREs than those without

~2x greater change in HA in patients with LREs

Manuscript in preparation.

HA often changes in tandem with PIIINP/TIMP-1

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Serial changes in ELF and individual analytes – 207 patients with Primary Sclerosing Cholangitis (PSC)

LREs	Timepoint	HA (Mean)	PIIINP (Mean)	TIMP-1 (Mean)	ELF (Mean)
Yes	Baseline	237.32	12.14	412.22	10.82
	1 Year	424.93	16.02	514.07	11.60
	Difference	79%	32%	25%	0.79
No	Baseline	100.38	9.79	314.81	9.52
	1 Year	141.50	10.42	315.21	9.75
	Difference	41%	6%	0%	0.23

Larger changes in ELF and individual markers in patients who develop LREs than those without

~2x greater change in HA in patients with LREs

Manuscript in preparation.

HA often changes in tandem with PIIINP/TIMP-1

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Change in ELF and individual markers after eradication of Hepatitis C Virus

Table II. Changes in biomarkers measured at baseline, end of treatment, and at 24 weeks after DAA therapy. P-values are for the comparison between baseline and 24 weeks after treatment.

Biomarkers	Baseline	End of treatment	24 weeks after treatment	P-value
Type IV collagen (ng/ml)	213±85	190±67	174±55	<0.0001
M2BPGi	4.8±3.5	2.7±2.0	2.2±1.8	<0.0001
FIB-4 index	5.31±3.82	4.36±2.79	4.24±3.09	<0.0001
ELF score	11.5±1.2	10.8±1.1	10.4±1.0	<0.0001
HA (ng/ml)	534±780	350±687	224±272	<0.0001
PIIINP (ng/ml)	15.3±7.7	12.7±8.3	10.6±5.3	<0.0001
TIMP-1 (ng/ml)	338±291	248±74	233±69	<0.0001

Values are presented as mean ± SD. M2BPGi, *Wisteria floribunda* agglutinin-positive Mac-2-binding protein; ELF, enhanced liver fibrosis score; FIB-4, Fibrosis-4; HA, hyaluronic acid; PIIINP, amino-terminal propeptide of type-III procollagen; TIMP-1, tissue inhibitor of metal-loproteinase type-1.

HA is a greater contributor to ELF change

Mean difference from baseline

HA	PIIINP	TIMP-1	ELF
-0.74	-0.28	-0.15	-1.16

Kawaguchi T, et al. 2021 Oct;15(4):215

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Change in ELF score is associated with differential LRE risk

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2071 Patients with F3-F4 MASH with ELF measurement at baseline and 1 year

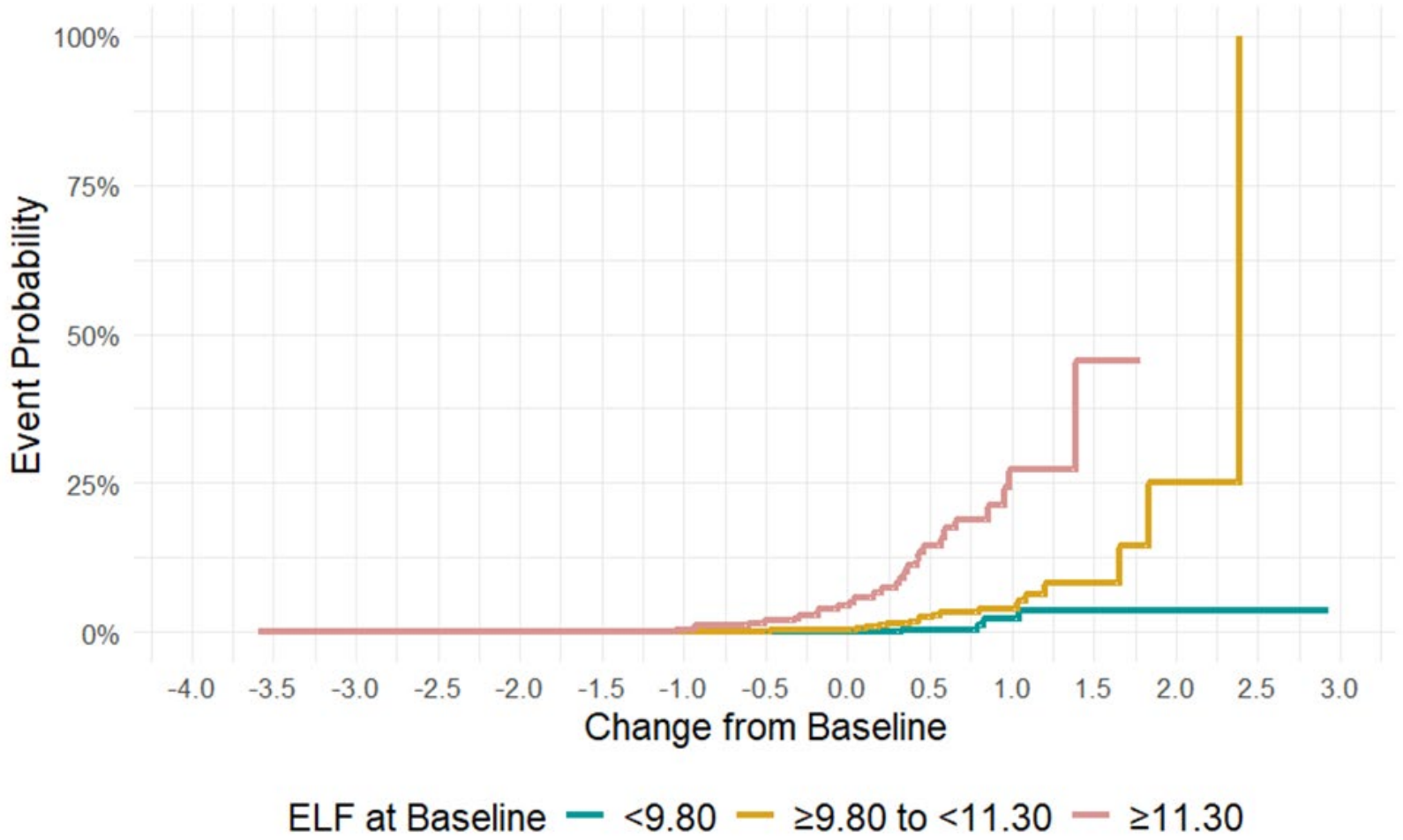
ELF Score (Baseline)	ELF Change at 1 Year	N	Patients with LRE	LRE Risk (95% CI)	Interval Likelihood Ratio (95% CI)	LREs per 1000 Patient Years (95% CI)
≥11.30	Δ ≥0.5	81	13	16.0% (8.8%, 25.9%)	4.31 (2.48, 7.49)	124.0 (57.2, 200.2)
	Δ >−0.5 to <0.5	201	26	12.9% (8.6%, 18.4%)	3.35 (2.35, 4.76)	98.8 (64.6, 136.7)
	Δ ≤−0.5	108	7	6.5% (2.6%, 12.9%)	1.56 (0.75, 3.26)	40.4 (11.5, 75.0)
≥9.80 to <11.30	Δ ≥0.5	284	18	6.3% (3.8%, 9.8%)	1.52 (0.99, 2.34)	42.3 (23.5, 63.4)
	Δ >−0.5 to <0.5	619	14	2.3% (1.2%, 3.8%)	0.52 (0.32, 0.85)	15.3 (7.7, 24.1)
	Δ ≤−0.5	169	2	1.2% (0.1%, 4.2%)	0.27 (0.07, 1.07)	7.5 (0.0, 18.7)
<9.80	Δ ≥0.5	225	6	2.7% (1.0%, 5.7%)	0.62 (0.28, 1.35)	17.4 (5.8, 32.0)
	Δ >−0.5 to <0.5	317	1	0.3% (0.0%, 1.7%)	0.07 (0.01, 0.50)	1.9 (0.0, 5.7)
	Δ ≤−0.5	67	1	1.5% (0.0%, 8.0%)	0.34 (0.05, 2.43)	8.8 (0.0, 26.3)

Patients can be stratified by ELF change at 1 year: declined (≤ -0.5), stable (> -0.5 to < 0.5), increased (≥ 0.5)

Association of LRE risk with ELF change at 1 year is dependent on baseline ELF score

Manuscript in preparation.

Change in ELF score is associated with differential LRE risk



2071 Patients with F3-F4 MASH
with ELF measurement at baseline and 1 year

Large changes in ELF are unlikely to significantly increase LRE risk if baseline ELF score is low.

Conversely, LRE risk is sensitive to small changes in ELF score if baseline ELF is high.

Association of LRE risk with ELF change at 1 year is dependent on baseline ELF score.

Manuscript in preparation.

Is ELF a potential reasonably likely surrogate endpoint?

Questions raised about ELF as RLSE

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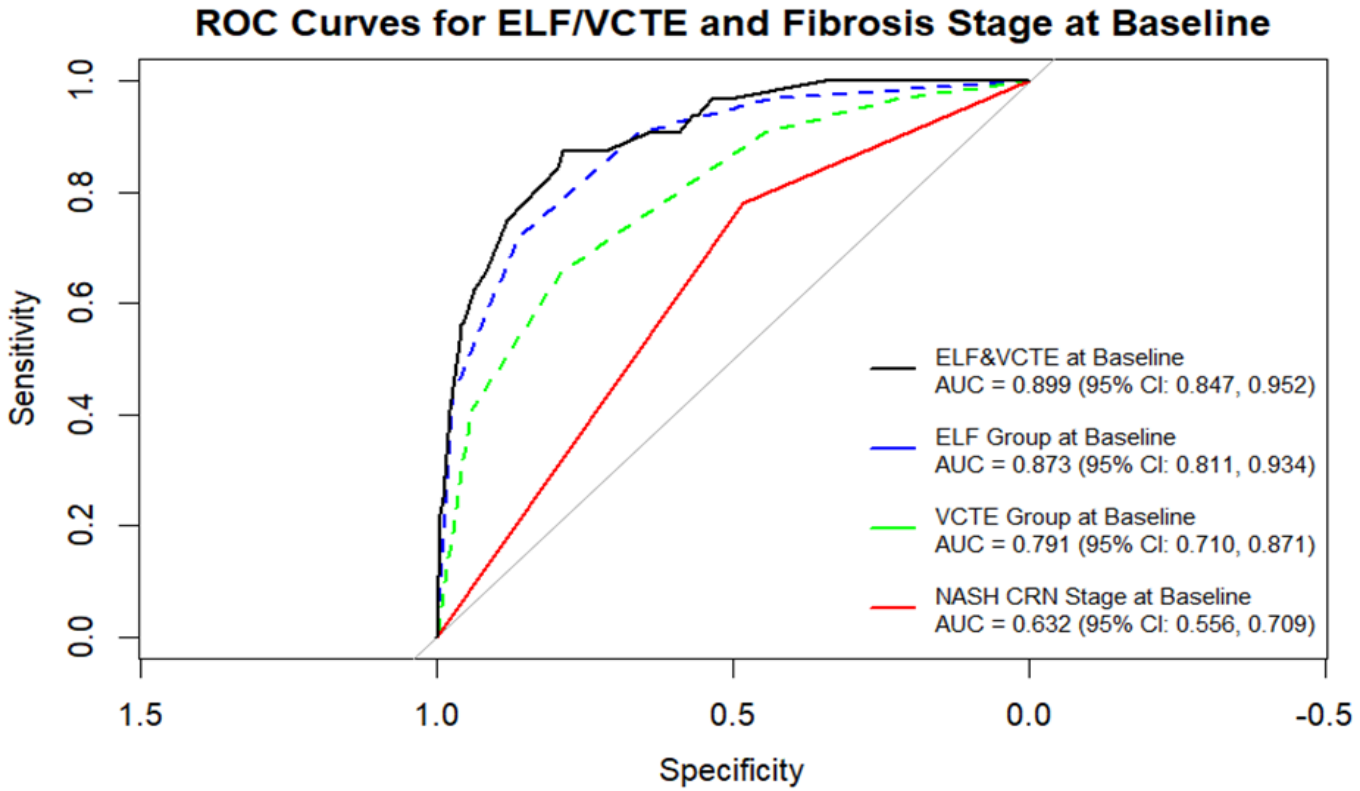
✓2. ELF performance in diabetics

✓3. ELF versus individual markers

✓4. Association of ELF change with change in LRE risk

5. Combination of ELF and VCTE

Combination of ELF and VCTE enhances LRE prognostication



452 Patients with F3-F4 MASH with 18 months of follow-up

Logistic regression modeling shows a combination of ELF & VCTE yields significantly higher AUROC than NASH CRN staging to predict LREs

Tests ≥Cutoff*	N	Patients with LREs	LRE Risk (95% CI)	Interval Likelihood Ratio (95% CI)
None	332	7	2.1% (0.9%, 4.3%)	0.28 (0.15, 0.55)
One	82	8	9.8% (4.3%, 18.3%)	1.42 (0.75, 2.68)
Both	38	17	44.7% (28.6%, 61.7%)	10.62 (6.26, 18.03)

*ELF 11:30; VCTE 30 kPa

Manuscript in preparation.

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✓5. Combination of ELF and VCTE

Summary

- Extensive evidence for ELF as a prognostic biomarker in MASH
- ELF cutoffs of 9.00, 9.80, 11.30, and 12.80 are validated for LRE risk assessment
- HA generally moves in tandem with PIIINP and TIMP-1 (in multiple etiologies)
- Suggestion that ELF score is directly influenced by glycemic control or diabetes status is not supported by evidence
- Preliminary findings that ≥0.5-unit change from baseline is associated with differential LRE risk
- ELF + VCTE outperform histological fibrosis stage for prognosticating LREs

ELF shows considerable promise as a Reasonably Likely Surrogate Endpoint in MASH clinical trials

Thank You

“Cooperation”

As interpreted by PowerPoint Stock Images

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