Meta-analysis of the performance of the Enhanced Liver Fibrosis (ELF) Test to identify significant fibrosis, advanced fibrosis and cirrhosis in patients with MASLD

Mathew F. W. Gee[1,2], Donald B. Chalfin[1,3], Edward B. De Vol[1], H. Roma Levy[1], Artem T. Boltyenkov[1], Mario Gutierrez Casale[1], Arun J. Sanyal[4]

[1]Siemens Healthcare Diagnostics Inc., Tarrytown, New York, United States; [2]Institute of Medical Science, Temerty Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada; [3]UCSF Medical School, University of California San Francisco, San Francisco, CA, United States; [4]Stavitz-Sanyal Institute for Liver Disease and Metabolic Health, Division of Gastroenterology, Hepatology and Nutrition, Virginia Commonwealth University School of Medicine, Richmond, Virginia, United States.

Introduction and aim

Non-invasive tests are increasingly employed to evaluate liver fibrosis associated with MASLD. The Enhanced Liver Fibrosis (ELF) Test is the first commercially available test of this type that specifically assesses fibrosis levels. Accurate ELF cut-offs for significant fibrosis (≥F2), advanced fibrosis (≥F3) and cirrhosis (F4) are critical for establishing diagnostic guidelines, evaluating disease severity, and qualifying patients for anti-fibrotic therapy. Previous meta-analyses evaluating cut-offs had methodological limitations, namely incorporating studies employing variable patient selection criteria (e.g. fibrosis stage determination by either elastography or biopsy), using histological staging systems not employing clear grading criteria, including heterogeneous populations comprised of patients with various fibrotic liver disease diagnoses, using off-the-shelf component assays or systems not validated for use with the manufacturer-derived algorithm, or using an inappropriate ELF algorithm for the system used to run the assays.

We conducted a meta-analysis (Prospero registration #1145859) to overcome the above limitations and to incorporate all MASLD-specific diagnostic threshold studies conducted between Jan. 1, 2004 (year of assay development) and May 10, 2024.

Methods

- PRISMA-compliant protocol. (Figure 1).
- Comprehensive database searches (EMBASE, PubMed, Cochrane, CINAHL).
- Well-defined *a priori* inclusion/exclusion criteria (Figure 2).
- QUADAS-2-assessment for risk of bias and applicability concerns (patient selection, index test, reference standard, flow and timing).
- Software R (version 4.4.2) with the "diagmeta" package.[1]
- Hierarchical summary ROC (HSROC) analysis to determine AUCs by integrating multiple thresholds per Steinhauser et al.[2]
- Study algorithm correction as needed using transforms per Gee et al (Figure 2).[3]

Results

- Individual ROC and summary ROC (SROC) curves were created for each stage-specific cohort using data supplied in each included study (Figure 3).
- HSROC analysis synthesized the multiple thresholds extracted from each study (Figure 4).
- The AUCs calculated by the HSROC process were calculated for each fibrosis stage cut-off(s), in addition to sensitivity, specificity, and 95% confidence intervals (CI; Tables 1 & 2, orange shading).
- PPVs and NPVs were calculated for a range of prevalences that might be found in different types of clinical practices (Tables 1 and 2).
- Cut-offs for balanced sensitivity and specificity and 95% CIs estimated using a bivariate random-effects model were generated (Youden indices) along with 95% CIs at the predetermined cut-off AUCs (Tables 1 & 2, blue shading).
- The 9.00 ELF cut-off yielded higher sensitivity than all other cut-offs and high NPV across the prevalence range, which is helpful for ruling out significant fibrosis intervals (Table1).
- The 9.80 cut-off yielded high specificity, which is helpful for identifying advanced fibrosis, and also yielded high NPV across the prevalence range, indicating that it is useful for ruling out advanced fibrosis as well (Table1).
- The 11.30 cut-off demonstrated high specificity for cirrhosis and higher PPVs across the prevalence range compared to the 9.00 and 9.80 cut-offs while retaining high NPVs across prevalences, validating its usefulness as a potential rule-in or rule-out test in practices with ≥20% MASLD prevalence, as might be expected in specialty care (Table 2).
- The newly defined 10.50 cut-off demonstrated higher sensitivity than the 11.30 cut-off while retaining >80% specificity as well as PPVs and NPVs comparable to the 11.30 cut-off, suggesting that this cut-off could serve as an upper limit for defining F3 disease (Table 2).

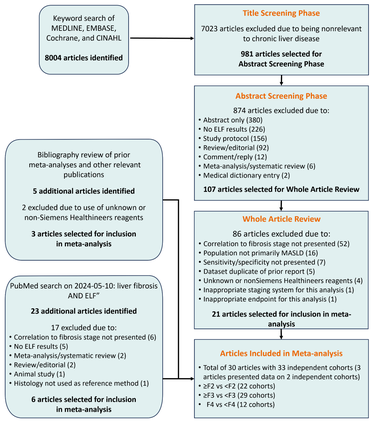

Figure 1. Flowchart outlining the study protocol.

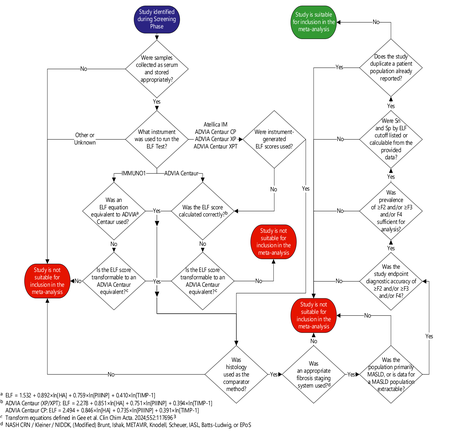

Figure 2. Flowchart outlining the *a priori* criteria for article selection.

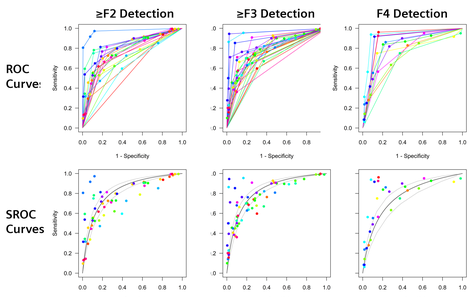

Figure 3. ROC and SROC curves for multiple thresholds for each fibrosis stage.

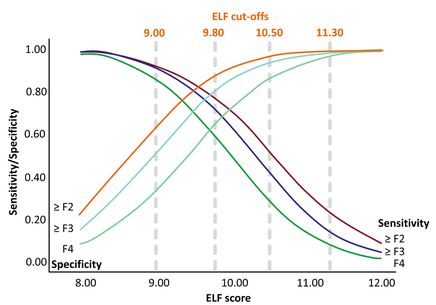

Figure 4. HSROC analysis for sensitivity and specificity across multiple thresholds.

Table 1. AUC, sensitivity, specificity, PPV, and NPV for ≥F2 and ≥F3 cut-offs across a range of prevalences possible in clinical practice.

	Cut-off	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Prevalence	PPV	NPV
≥F2	9.00	0.83 (0.79, 0.86)	0.86 (0.80, 0.90)	0.63 (0.52, 0.73)	0.05	0.11	0.99
					0.10	0.20	0.98
					0.20	0.37	0.95
					0.30	0.50	0.91
					0.40	0.61	0.87
					0.50	0.70	0.81
					0.70	0.84	0.65
	9.34[a] (9.24, 9.44)[b]	0.83	0.76 (0.69, 0.82)	0.76 (0.67, 0.83)	0.05	0.14	0.98
					0.10	0.26	0.97
					0.20	0.44	0.93
					0.30	0.57	0.88
					0.40	0.68	0.83
					0.50	0.76	0.76
					0.70	0.88	0.58
≥F3	9.63[a] (9.54, 9.72)[b]	0.83	0.77 (0.70, 0.82)	0.76 (0.68, 0.82)	0.05	0.14	0.98
					0.10	0.26	0.97
					0.20	0.44	0.93
					0.30	0.57	0.88
					0.40	0.68	0.83
					0.50	0.76	0.76
					0.70	0.88	0.58
	9.80	0.83 (0.79, 0.86)	0.71 (0.63, 0.77)	0.81 (0.74, 0.86)	0.05	0.20	0.98
					0.10	0.29	0.96
					0.20	0.48	0.92
					0.30	0.61	0.87
					0.40	0.71	0.81
					0.50	0.79	0.73
					0.70	0.90	0.54

a. Youden index
b. Youden index CI

Table 2. AUC, sensitivity, specificity, PPV, and NPV for F4 cut-offs across a range of prevalences possible in clinical practice.

	Cut-off	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Prevalence	PPV	NPV
F4	10.00[a] (9.87, 10.13)[b]	0.77	0.70 (0.59, 0.79)	0.73 (0.63, 0.80)	0.05	0.12	0.98
					0.10	0.22	0.96
					0.20	0.39	0.91
					0.30	0.52	0.85
					0.40	0.63	0.78
					0.50	0.72	0.71
					0.70	0.86	0.51
	10.50	0.77 (0.71, 0.83)	0.51 (0.40, 0.62)	0.86 (0.80, 0.90)	0.05	0.28	0.96
					0.10	0.29	0.94
					0.20	0.48	0.88
					0.30	0.61	0.80
					0.40	0.71	0.73
					0.50	0.78	0.64
					0.70	0.89	0.43
	11.30	0.77 (0.71, 0.83)	0.22 (0.16, 0.30)	0.96 (0.94, 0.97)	0.05	0.31	0.95
					0.10	0.39	0.92
					0.20	0.58	0.83
					0.30	0.70	0.74
					0.40	0.79	0.65
					0.50	0.85	0.55
					0.70	0.93	0.35

a. Youden index
b. Youden index CI

Conclusions

- The ELF Test identifies significant fibrosis, advanced fibrosis, and cirrhosis in patients with suspected MASLD/MASH.
- A cut-off of 9.0 could be useful for ruling out patients who do not have significant fibrosis, and an ELF value of 9.80 represents a balanced cut-off to identify advanced fibrosis.
- An ELF value of 11.30 is a high-specificity rule-in cut-off.
- An ELF value of 10.50 may be beneficial as a higher sensitivity threshold to identify patients with suspected cirrhosis.

References

1. R Core Team. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing. Available at R: The R Project for Statistical Computing
2. Steinhauser S et al. BMC Med Res Methodol. Aug 12 2016;16(1):97. doi:10.1186/s12874-016-0196-1
3. Gee MFW, et al. Clin Chim Acta. Jan 1 2024;552:117696. doi:10.1016/j.cca.2023.117696

Scan the QR code for a downloadable copy of the poster and hear exclusive insights from Dr. Sanyal on this research and its clinical impact.

www.medicalaffairs.siemens-healthineers.com

For education and scientific exchange only. Not for sales or promotional use.

Published by Siemens Healthcare Diagnostics Inc. 11-2025