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Cost-effectiveness of blood-based non-invasive testing strategies for metabolic dysfunction-associated steatotic liver disease (MASLD) in a veteran population

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Background/Aim

Non-invasive tests (NITs) have emerged as promising tools for staging liver fibrosis, along with the determination of patient risk profiles and the creation of evidence-based care pathways for individuals with or at risk of developing or having MASLD. In contrast to liver biopsy, NITs can provide safer, more accessible, and potentially more cost-effective ways to assess liver fibrosis and track disease progression (Srivastava et al., 2019; Congly et al., 2021; Kjaergaard et al., 2023). NITs commonly used in clinical practice for fibrosis staging and patient follow-up can be grouped into blood-based tests and imaging techniques.

The most frequently used blood-based NITs are the fibrosis index based on four factors (FIB-4 index) and the Enhanced Liver Fibrosis (ELF™) test, which generates a unitless value calculated from three assays measuring direct markers of fibrogenesis (hyaluronic acid, amino-terminal propeptide of type III procollagen) and fibrinolysis (tissue inhibitor of matrix metalloproteinase 1). The most frequently used imaging methods used for diagnosis include vibration-controlled transient elastography (VCTE) and magnetic resonance elastography (MRE). Despite method-specific limitations such as accuracy, availability, accessibility, cost, lack of standardization, and limited long-term data on predictive ability, it is well accepted that NITs offer valuable information about the degree of liver fibrosis, enabling clinicians to make informed decisions regarding patient management and treatment strategies. The European Association for the Study of the Liver (EASL), the American Association for the Study of Liver Diseases (AASLD), and the American Gastroenterology Association (AGA) recommend the use of a combination of NITs as an alternative to liver biopsy for fibrosis staging, patient follow-up and management (Berzigotti et al., 2021; Rinella et al., 2023; Kanwal et al., 2021; Long et al., 2022). However, there is currently no accepted consensus on which, if any, NIT-based strategies yield the best performance for early detection of advanced liver fibrosis (stages F3/F4) in MASLD. Lack of consensus results in both unnecessary referrals to hepatologists for patients with a low likelihood of progression to advanced liver fibrosis, and delayed referrals or long waiting times for patients who are in greater need of specialist care.

Patients in primary care and endocrinology practices often do not have easy, cost-effective access to imaging techniques as these technologies are typically limited to specialty locations and tertiary care centers in predominantly major urban centers. Therefore, in this study we focused on comparing cost-effectiveness of blood-based NIT strategies that can be conducted easily within primary and endocrine practices, regardless of location, due to the generally easy access to phlebotomy and laboratory services. As the prevalence of MASLD continues to rise and NITs become increasingly incorporated into clinical practice, it is important to compare the cost-effectiveness of incorporating different blood-based NIT strategies into clinical practice. The primary goal of this study was to evaluate the cost-effectiveness of six blood-based NIT-based strategies from the healthcare perspective.

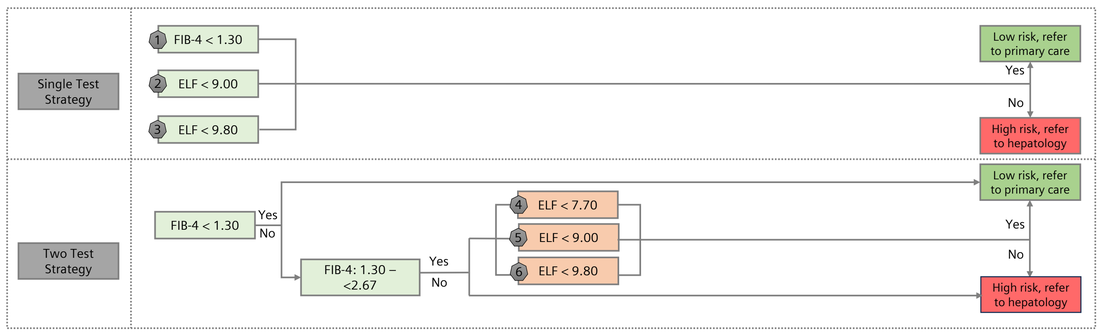

Figure 1. Illustration of the referral pathways for the one and two test scenarios.

Methods

This cost-effectiveness analysis utilized patient-level information from a larger prospective cohort study currently underway at the Veteran Affairs Palo Alto Healthcare System (VAPAHCS) in Palo Alto, CA. This study was funded by Siemens Healthineers. Siemens Healthineers employees were involved in the study design, conduct, and reporting of the analysis. Briefly, a prospective cohort study was designed to evaluate the performance of select NITs to improve the screening and monitoring of hepatic fibrosis among patients at risk for MASLD. The electronic medical records (EMR) of patients receiving care at the VAPAHCS were examined to identify at-risk individuals with a body mass index (BMI) > 30 and/or those who received medication for type 2 diabetes mellitus (T2DM).

Eligible participants (N=254) underwent serum biomarker screening by the Fibrosis-4 (FIB-4) index and the Enhanced Liver Fibrosis (ELF) test. A decision analytic model was developed to project health care costs and lifetime quality-adjusted life years (QALYs) for adult patients at risk of MASLD. Costs and quality-of-life values were estimated from published research. A cost-effectiveness analysis (CEA) was conducted to compare 6 testing strategies in this population, including FIB-4 alone at 1.3 cut-off, ELF alone with 9.00 and 9.80 cut-offs, and FIB-4 followed by ELF with 7.70, 9.00 and 9.80 cut-offs.

For each of the six blood-based strategies, patients were categorized as either low- or high-risk for significant fibrosis (≥F2) based on the scores generated from the blood-based NIT strategies. Patients with FIB-4 <1.30 (FIB-4 only), ELF < 9.00 or ELF < 9.80 (two separate ELF alone strategies) were considered at low risk for advanced fibrosis (F3/F4) in the single-test strategies (strategies 1–3) (Mozes et al., 2022). Conversely, patients with FIB-4 ≥1.30 (FIB-4 only), ELF ≥ 9.00, ELF ≥ 9.80 (two separate ELF alone strategies) were considered high risk. In the two-test strategies, patients were initially screened using FIB-4. A second test using ELF with the thresholds 7.70, 9.00 and 9.80 was added if the initial test gave an indeterminate result for FIB-4 (1.30-2.67) forming three two-test strategies, one for each of the ELF thresholds.

In all scenarios, patients in the low-risk group were considered at low risk of advanced fibrosis (F3/F4) and were advised to follow up with their primary care physician or endocrinologist for lifestyle modification counselling and monitoring. Patients in the high-risk group were considered at high risk of advanced fibrosis and were referred to a hepatologist for additional testing and fibrosis staging.

We developed a microsimulation model to assess the cost-effectiveness of each blood-based NIT strategy (TreeAge Pro Healthcare, version 2023). The microsimulation model included Probabilistic Sensitivity Analysis (PSA) based on the test scores of each individual patient from the cohort, and the cost, transition probabilities and utility information taken from the literature. A total of 254 1st order simulation trials were run on 1,000 2nd order parameter samples, using a lifetime time

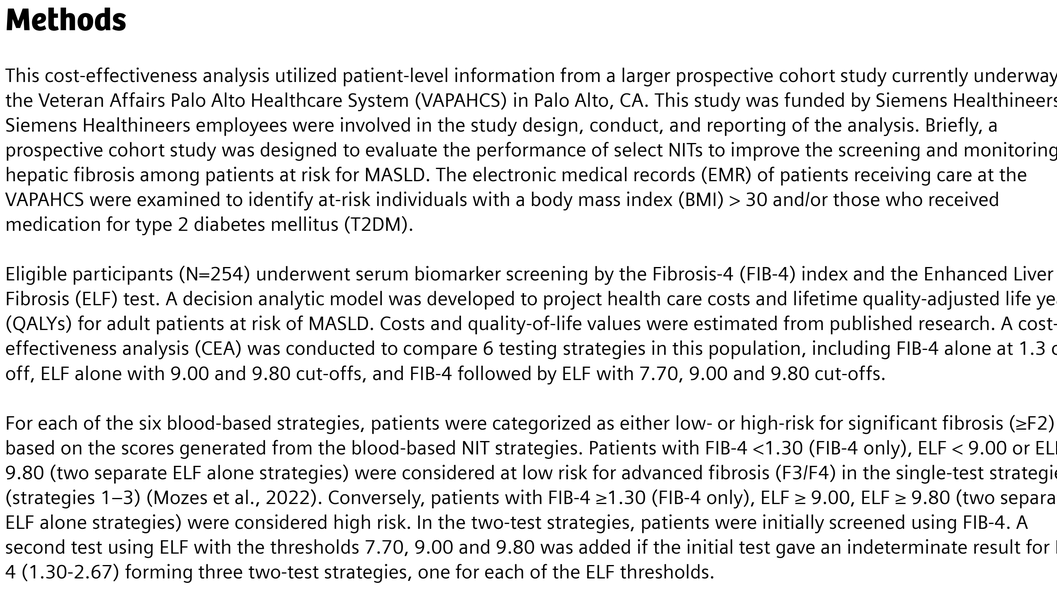

Figure 2. CE Acceptability Curve. Illustrates cost-effectiveness acceptability curves at different WTP thresholds.

Table 1. Distribution of patients remaining in primary care, referrals to hepatology, and the corresponding associated costs for each NIT strategy.

NIT Strategy	Strategy	Patients Remaining in Primary Care	Cost of Non-referral/Patient	Number of Referrals to Hepatologist	Cost of Referral/Patient	Cost of Strategy/ Patient
FIB-4 only	1	63.1%	$82.97	36.9%	$1,064.91	$445.35
ELF only (9.00 cut-off)	2	15.4%	$259.16	84.6%	$1,241.10	$1,089.70
ELF only (9.80 cut-off)	3	48.5%	$259.16	51.5%	$1,241.10	$765.27
FIB-4/ELF (7.70 cut-off)	4	61.7%	$82.97	38.3%	$1,207.20	$513.84
FIB-4/ELF (9.00 cut-off)	5	63.9%	$89.04	36.1%	$1,206.20	$492.60
FIB-4/ELF (9.80 cut-off)	6	72.7%	$109.66	27.3%	$1,200.58	$407.62

Results

Patients (N=254) were enrolled with a mean age 65.3+/-9.3 years, and a mean body mass index (BMI) of 31.7+/-6. Of these patients, 87.4% were male, 78.3% non-Hispanic, and 96.5% had T2DM.

We simulated 254 patients from our cohort of VAPAHCS patients with 1,000 parameter samples for each patient. In 50.50% of all simulations the FIB-4/ELF with the 9.80 cut-off strategy was the most cost-effective, while in only 0.4% of all simulations the ELF alone strategy with the 9.00 cut-off was the most cost-effective. The prior standard of care at VAPAHCS, a single test FIB-4 strategy was the most cost-effective in 21.90% of simulations.

Total costs per person were lowest for the FIB-4/ELF with the 9.80 cut-off ($28,474) and highest for the ELF alone strategy with the 9.00 cut-off ($35,008). The prior standard of care, FIB-4 strategy had a cost of $29,623. Lifetime QALYs were lowest for ELF alone strategy with 9.00 cut-off (13.52) and highest for FIB-4/ELF with the 9.80 cut-off strategy (14.24). FIB-4 strategy has a lifetime QALY of 14.09. In addition, FIB-4/ELF with the 9.80 cut-off strategy yielded the longest life years at 15.01 years and the highest net monetary benefit (NMB) at $100,000 willingness to pay (WTP) threshold at $1,395,330. Conversely, ELF alone strategy with 9.00 cut-off yielded the shortest life years at 14.17 years and the lowest NMB at $100,000 WTP threshold at $1,316,817. FIB-4 strategy had 14.84 life years and NMB of $1,379,092. The ranking of strategies remained unchanged also at WTP threshold at $50,000.

The CEA revealed that the FIB-4/ELF with 9.80 cut-off strategy dominated all other blood-based non-invasive strategies.

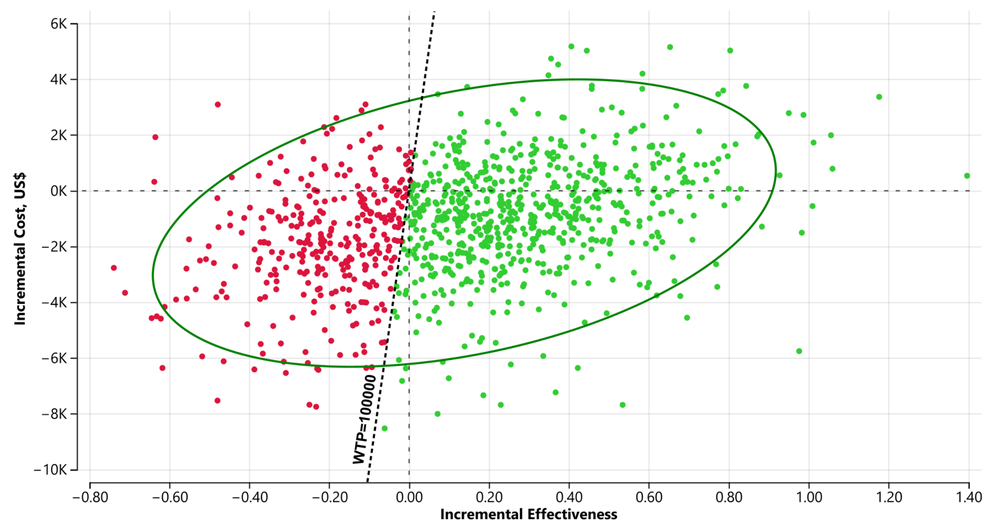

Figure 3. Incremental cost-effectiveness scatterplot comparing the most cost-effective FIB-4/ELF with 9.80 cutoff threshold strategy with the prior standard of care at VAPAHCS FIB-4 strategy. Red dots indicate FIB-4 strategy is best while green dots indicate FIB-4/ELF with 9.80 cutoff threshold is best.

Table 2. Results of the microsimulation analysis of 254 1st order simulation trials run on 1,000 2nd order parameter samples.

Willingness-to-Pay	Strategy	Acceptability (%)
$100,000	FIB-4/ELF 9.80	50.5
	FIB-4	21.9
	ELF 9.80	14.2
	FIB-4/ELF 9.0	7.1
	FIB-4/ELF 7.70	4.9
	ELF 9.00	0.8
	Indifferent (+/-0.01)	0.6
$50,000	FIB-4/ELF 9.80	53.3
	FIB-4	21.2
	ELF 9.80	13
	FIB-4/ELF 9.00	7.2
	FIB-4/ELF 7.70	4.3
	ELF 9.00	0.6
	Indifferent (+/-0.01)	0.4

Conclusions

- FIB-4 followed by ELF with the 9.80 cut-off strategy can be a cost-effective gatekeeping tool in veteran patients at risk for MASLD in the United States in primary care and endocrinology settings.
- This study's primary strength lies in the utilization of the combination of real-world patient data with microsimulation for the cost-effectiveness analysis of blood-based NIT strategies.
- This combination of analyses compared the long-term cost-effectiveness of blood-based NIT strategies in patients at risk of MASLD in primary care and endocrinology settings.
- Future studies comparing different NIT strategies across diverse data resources from multiple centers is needed to enable more generalizable findings that will apply to a broader patient population likely to be afflicted by MASLD for both short-term and long-term assessments.

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