



Cost-Comparison Analysis of Non-invasive Testing Strategies for Metabolic Dysfunction-Associated Steatohepatitis (MASH) 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, N-terminal protein of procollagen type 3) and fibrinolysis (tissue inhibitor of metalloproteinase 1). The most frequently used imaging NITs include vibration-controlled transient elastography (TE) 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 hepatology for patients with a low likelihood of progression to advanced liver fibrosis and delayed referrals for patients who are more likely to benefit.

As the prevalence of MASLD continues to rise and NITs become increasingly incorporated into clinical practice, it is important to compare the diagnostic performance and cost impact of incorporating different NIT strategies into clinical practice in terms of their ability to triage referrals to hepatologists. The primary goal of this study was to evaluate the referral patterns of ten NIT-based strategies and compare referral rates and associated costs using data collected in a real-world study.

Methods

This retrospective 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 T2DM.

Eligible participants (N=254) underwent serum biomarker screening by the Fibrosis-4 (FIB-4) index, the Enhanced Liver Fibrosis (ELF) test, and vibration-controlled transient elastography (VCTE). A subset of patients (N=59) selected on the basis of FIB-4 index scores underwent magnetic resonance elastography (MRE). A total of ten NIT strategies categorized into single-test, two-tests, and three-tests were evaluated for referrals rates to secondary care and cost savings.

For each of the ten strategies, patients were categorized as either low- or high-risk for significant fibrosis (≥F2) based on the scores generated from the NIT strategies. Patients with FIB-4 <1.3 (FIB-4 only), ELF < 9.0 (ELF only), or TE < 8.0 kPa (TE only) 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 ≥1.3 (FIB-4 only), ELF ≥ 9.0 (ELF only), or TE ≥ 8.0 kPa (TE only) were considered high risk. In the two- and three-test strategies, patients were initially screened using either FIB-4 or ELF. A second test using ELF, TE, or MRE was added if the initial test gave an indeterminate result for FIB-4 (1.30-2.67) or an indeterminate result for ELF (9.0-10.5). In the three test strategies, imaging was conducted if the second-line ELF test yielded a score between 9.0 and 10.5.

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.

Results

Patients (N=254) were enrolled: mean age 65.3±9.3 years, mean body mass index (BMI) of 31.7±6, 87.4% male, 78.3% non-Hispanic/Latino, 96.5% had type 2 diabetes mellitus (T2DM). Four out of ten strategies showed lower referral rates and lower costs than the FIB-4 only strategy. The strategies yielding the highest proportion of patients remaining in primary care were FIB-4/MRE (51/58; 87.9%), FIB-4/TE (199/230; 86.5%), FIB-4/ELF/TE: (161/205; 78.5%), and FIB-4/ELF (165/227; 72.7%). The costs per-patient associated with each strategy were: \$408.35 (FIB-4/MRE), \$225.64 (FIB-4/TE), \$322.99 (FIB-4/ELF/TE), and \$411.70 (FIB-4/ELF). Using FIB-4 alone resulted in 63.1% (93/252) of patients being kept within primary care and \$445.35 per-patient costs.

- **Figure 1** illustrates the referral pathways for the one, two, and three test scenarios.
- **Table 1** presents data on the distribution of patients remaining in primary care, referrals to hepatology, and the corresponding associated costs for each NIT strategy.
- **Table 2** provides information regarding the distribution of patients who either continue their care in the primary care or are referred to hepatology at the conclusion of the first, second-tier, and third-tier assessments for each NIT strategy.

Figure 1.

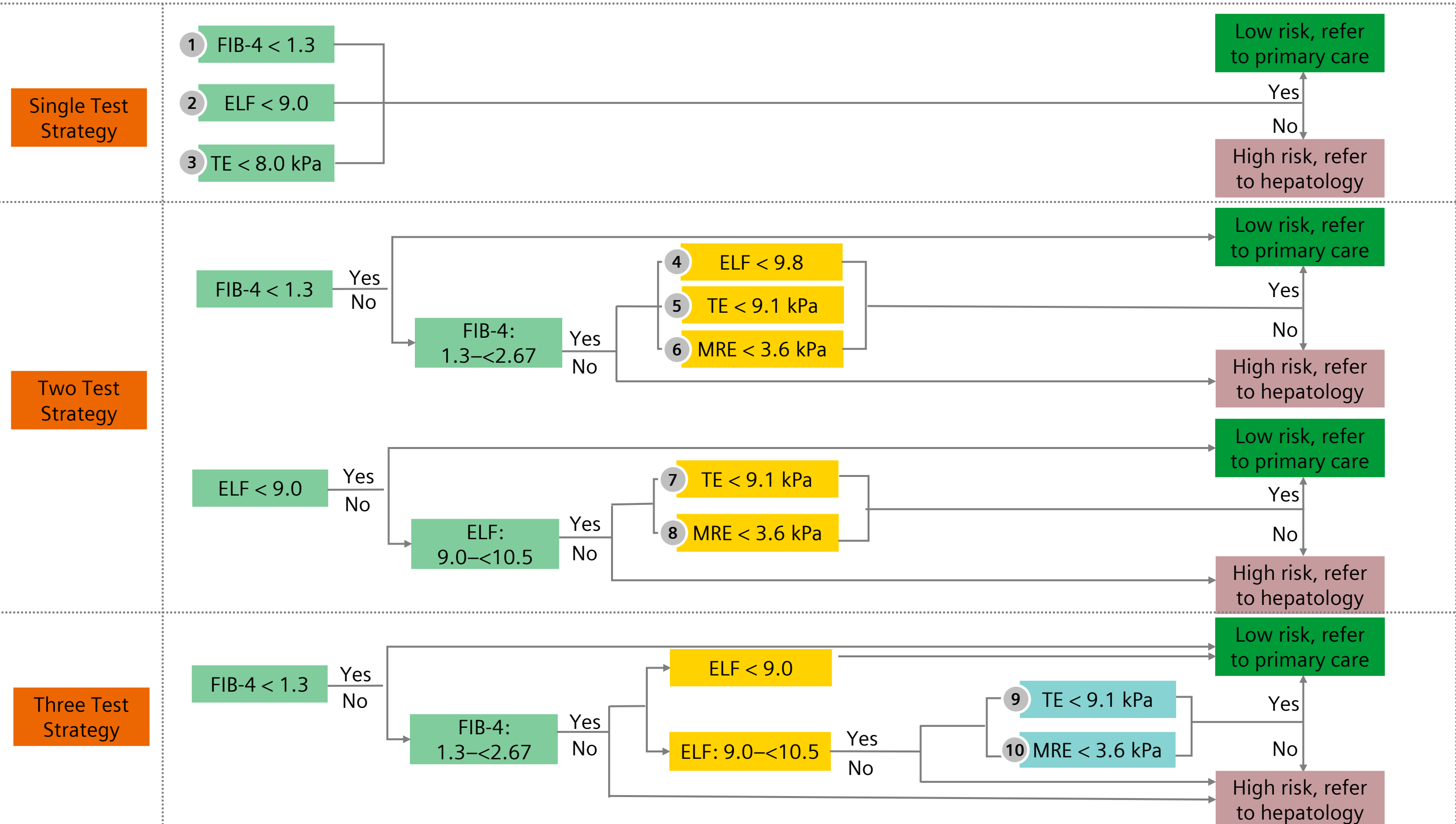


Table 1.

NIT Strategy	n1_Test1	p1_PC	p1_Referred	n2_Test2	P2_PC	P2_Referred	n3_Test3	p3_PC	P3_Referred
FIB-4 only	252	63.1%	36.9%	-	-	-	-	-	-
ELF only	227	15.4%	84.6%	-	-	-	-	-	-
TE only	227	65.2%	34.8%	-	-	-	-	-	-
FIB-4/ELF	227	61.7%	4.0%	78	32.1%	67.9%	-	-	-
FIB-4/TE	227	62.6%	3.9%	77	71.4%	28.6%	-	-	-
FIB-4/MRE	58	24.1%	8.6%	39	94.9%	5.1%	-	-	-
ELF/TE	203	15.6%	20.5%	131	67.9%	32.1%	-	-	-
ELF/MRE	58	13.8%	31.0%	32	96.9%	3.1%	-	-	-
FIB-4/ELF/TE	203	61.0%	3.9%	72	5.6%	30.6%	46	69.6%	30.4%
FIB-4/ELF/MRE	58	24.1%	8.6%	39	5.1%	35.9%	23	95.7%	4.3%

Table 2.

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	2	15.4%	\$259.16	84.6%	\$1,241.10	\$1,089.70
ELF only (9.8 threshold)	2a	48.5%	\$259.16	51.5%	\$1241.10	\$765.27
TE only	3	65.2%	\$113.81	34.8%	\$1,095.75	\$455.35
FIB-4/ELF	4	72.7%	\$109.66	27.3%	\$1,215.52	\$411.70
FIB-4/TE	5	86.5%	\$91.49	13.5%	\$1,086.79	\$225.64
FIB-4/MRE	6	87.9%	\$306.17	12.1%	\$1,152.81	\$408.35
ELF/TE	7	59.0%	\$281.84	41.0%	\$1,256.52	\$681.22
ELF/MRE	8	67.2%	\$503.70	32.8%	\$1,257.29	\$750.57
FIB-4/ELF/TE	9	78.5%	\$93.48	21.5%	\$1,162.82	\$322.99
FIB-4/ELF/MRE	10	65.5%	\$270.36	34.5%	\$1,203.62	\$592.17

n1=number of patients getting test1
n2=number of patients getting test2
n3=number of patients getting test3
p1_PC=proportion of patients remaining in primary care after test 1
p2_PC=proportion of patients remaining in primary care after test 2
p3_PC=proportion of patients remaining in primary care after test 3
p1_referred=proportion of patients referred to hepatologist after test 1
p2_PC=proportion of patients referred to hepatologist after test 2
p3_PC=proportion of patients referred to hepatologist after test 3

Conclusions

- Among the strategies assessed, four strategies (FIB-4/MRE, FIB-4/TE, FIB-4/ELF/TE, and FIB-4/ELF) resulted in lower referral rates to hepatology clinics and lower costs compared to the FIB-4 only strategy. These four strategies, in comparison to the FIB-4-only strategy, realized substantial cost savings, ranging from 7.56% to 49.33%.

- This study's primary strength lies in its utilization of real-world patient data and suggesting the value of NITs as screening approaches 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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