Oral targeted therapy for the treatment of non–small cell lung carcinoma

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Key points

- Targeted cancer therapies are a group of oral medications directed at tumours harbouring specific driver mutations that occur in a subset of patients with cancer.
- Around one-third to one-half of patients with advanced non–small cell lung carcinoma may harbour an actionable mutation, which can be identified from molecular analysis of a biopsy or surgical specimen.
- Patients treated with targeted therapy generally have better symptom control, response rates (i.e., shrinking tumours), and overall survival than those treated with conventional chemotherapy.
- Targeted therapy is typically well tolerated and does not carry the same risks of emesis, alopecia, immunosuppression, and febrile neutropenia as chemotherapy.

Table 2: Adverse effects related to targeted therapy classes, grouped by their target gene*

Target gene	Common adverse effects	Serious adverse effects
KRAS (G12C)	Fatigue, nausea, diarrhea, elevated liver enzymes, arthralgias	Pneumonitis
EGFR	Rash, nail changes, diarrhea	Pneumonitis, cardiomyopathy
ALK	Laboratory abnormalities (elevation in cholesterol or triglycerides, creatine kinase, and glucose), peripheral edema, diarrhea, cognitive changes‡	Bradycardia, pneumonitis
BRAF	Pyrexia, nausea, diarrhea, hypertension	Cardiomyopathy
MET	Peripheral edema, nausea, dyspnea, elevated creatinine, elevated amylase without pancreatitis§	Pneumonitis, pleural effusions
ROS1†	Diarrhea, nausea, visual changes, elevated liver enzymes, hypophosphatemia	–
RET	Diarrhea, dry mouth, hypertension, nausea, peripheral edema, hyponatremia	–
NTRK	Fatigue, constipation, dysgeusia, dizziness, dysesthesia, mood changes, peripheral edema	Mood disorder, increased risk of fractures (falls)

*List of adverse effects is not exhaustive; adverse effects may vary depending on the exact drug used.
†In some instances, neurotrophic tyrosine receptor kinase inhibitors (e.g., entrectinib) are also used for patients with mutations in *ROS1* fusion genes; shared adverse effects are listed under *NTRK*.
‡Adverse effects vary substantially from drug to drug.
§Peripheral edema may be substantial.

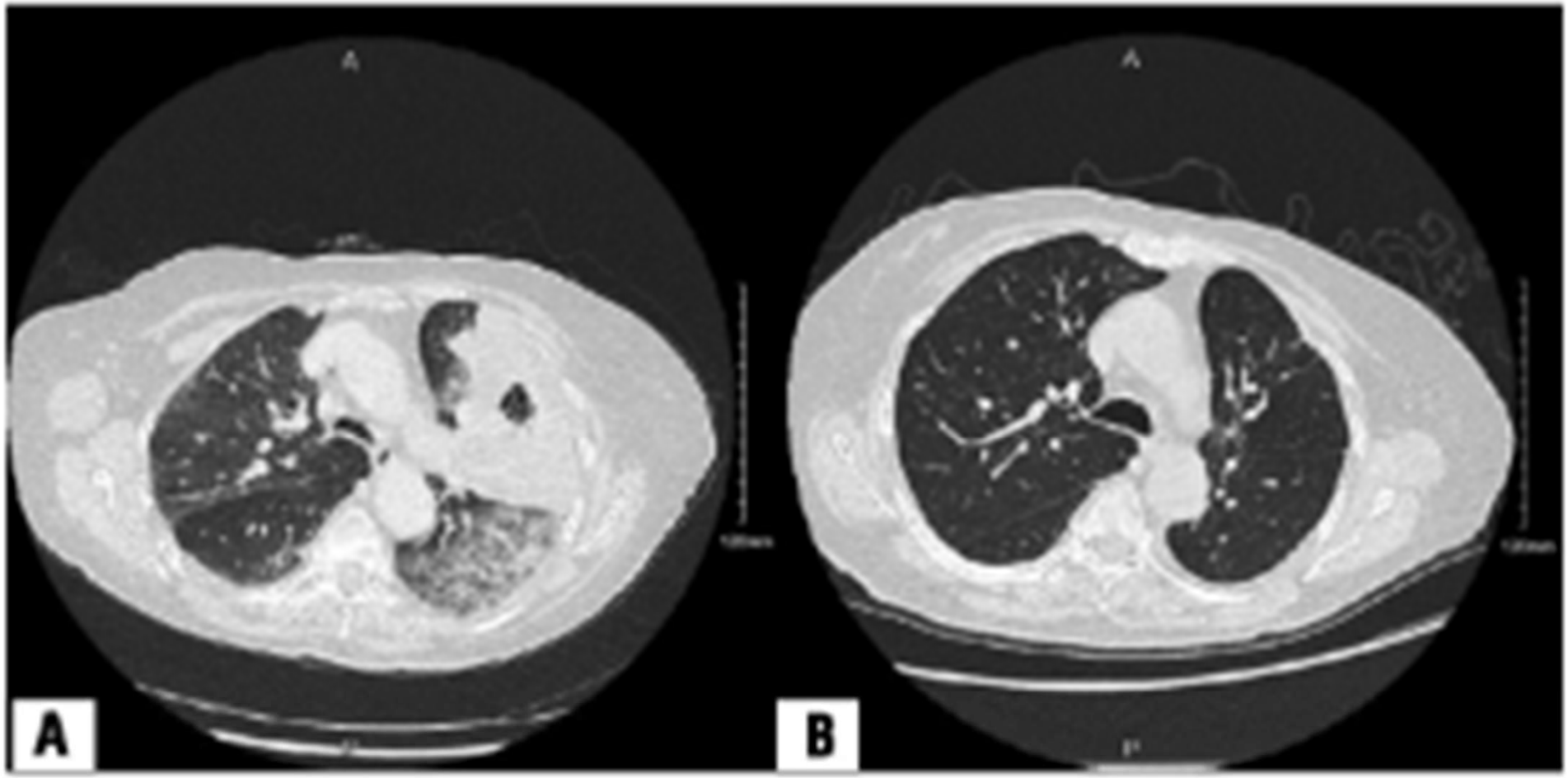

Figure 2: Axial computed tomography (CT) chest scans of a female patient in her late 80s, diagnosed with metastatic lung adenocarcinoma harbouring a *RET* rearrangement (*ERC1* exon 17 to *RET* exon 12) treated with selpercatinib (A) at the time of diagnosis and (B) 9 months after starting therapy, showing radiographic response below the aortic arch.

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LETTER TO THE EDITOR

AP&T Alimentary Pharmacology & Therapeutics WILEY

Letter: Association of persistently high HBsAg levels during HBeAg-seropositive stage and hepatocellular carcinoma risk in chronic hepatitis B patients—Authors' reply

Editors,

We appreciate the opportunity to discuss the issues raised concerning our article[1,2] on lower hepatocellular carcinoma (HCC) development in patients with persistent high hepatitis B surface antigen (HBsAg) levels who were hepatitis B e antigen (HBeAg)-positive with chronic hepatitis B.

First, regarding the questions about the association between hepatitis B virus (HBV) DNA levels, HBsAg levels and the severity of liver fibrosis, studies have shown that lower levels of HBsAg and HBV DNA in HBeAg positive CHB patients may be associated with more significant liver fibrosis.[3-5] Our study includes data on liver fibrosis, derived from a community-based cohort. Since significant liver fibrosis or cirrhosis is a major risk factor for the development of hepatocellular carcinoma, involving prolonged inflammation and regeneration, it is pertinent to our investigation. In our study, cases with persistently high HBsAg levels exhibited a lower percentage of abnormal alanine aminotransferase (ALT) levels, and follow-up assessments revealed a lower percentage of cirrhosis, indicating that inflammation was less prevalent in this group. Hence, although fibrosis levels were not thoroughly evaluated in our study, evidence of less inflammation and a reduced risk of HCC development could still be observed.

Second, our study showed the difference in BMI was not statistically significant between the persistent high HBsAg level group and the non-stationary group. Lastly, family history of HCC was also considered as a potential risk factor for the development of HCC. In the persistent high HBsAg level group, 5 out of 72 patients had a family history of HCC (6.9%), which is comparable to that in the non-stationary group, where 13 out of 247 patients had a family history of HCC (5.3%). In univariate analysis, family history of HCC was not significantly associated with the development of HCC (hazard ratio: 1.27 (95% CI: 0.40–4.03), $p=0.689$).

AUTHOR CONTRIBUTIONS

Hsin-Che Lin: Writing – original draft. **Wen-Juei Jeng**: Writing – review and editing. **Hwai-I Yang**: Writing – review and editing.

LINKED CONTENT

This article is linked to Lin et al papers. To view these articles, visit https://doi.org/10.1111/apt.17915 and https://doi.org/10.1111/apt.17971

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completely repressed, and serum concentrations are correspondingly very low.

From the time of birth onwards, α-FP is synthesized almost exclusively by malignant hepatocytes, although not all of these cells produce and secrete the protein.[4] The molecular mechanism responsible for the reintroduction of synthesis of the protein has yet to be uncovered, but it appears to be the result of increased gene transcription.[5] Production of α-FP by malignant hepatocytes is permanent, irrespective of the serum concentration attained,[6] although the level may decrease precipitously shortly before death. However, not all malignant hepatocytes produce and secrete α-FP, and the reason for this is not known.

The measurement of the serum concentration of α-FP as a confirmation of a clinical diagnosis of hepatocellular carcinoma (HCC) was introduced into clinical practice in the 1970s,[4] with a serum level greater than 500 ng/mL being generally regarded as being diagnostic of the presence of the tumor, although some centers used concentrations of 400 ng/mL and others of 200 ng/mL.

During the past approximately 14 years, however, doubt has been cast on the validity of using α-FP as a diagnostic marker of HCC in the serum of patients in low incidence regions of the tumor.[7–9] It was realized that a high proportion of HCCs identified using the sophisticated imaging techniques now available showed either the α-FP level to be within the normal range or, if raised above this range, then only raised to a slight or moderate degree in patients in these urban regions.[7]

By contrast, rural sub-Saharan Black Africans with high incidences of HCC and very limited imaging facilities available have not been subjected during recent years

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EDITOR

Whither α-FP in the diagnosis of hepatocellular carcinoma?

α-FP is an α_1-globulin present in high concentration in the fetal serum of mammals. It is the dominant plasma protein in the developing embryo, and is synthesized by the embryonal liver, by the endodermal cells of the visceral yolk sac, and, in very small amounts, by the embryonal intestine.[1] Approximately 80% of fetal hepatocytes synthesize and secrete α-FP. The protein has been closely conserved throughout phylogenesis, suggesting that it has functions essential to the fetus, although precisely what these functions are remains to be learned. There does, however, appear to be an inverse relationship between serum α-FP and albumin levels, suggesting that α-FP might function as fetal albumin.[2] Other possible biological properties of the α_1-globulin include binding to estrogens and bilirubin, immunosuppressive activity, and a growth-promoting potential.[3] The serum level of the protein remains constant until week 32, when it begins to sharply decrease. After birth, production of α-FP normally remains completely repressed, and serum concentrations are correspondingly very low.

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Insights into I

ORIGINAL ARTICLE Open

2D shear wave elastography (SWE) performance versus vibration-controlled transient elastography (VCTE/fibroscan) in the assessment of liver stiffness in chronic hepatitis

Ahmed M. Osman*, Ahmed El Shimy and Mohamed M. Abd El Aziz

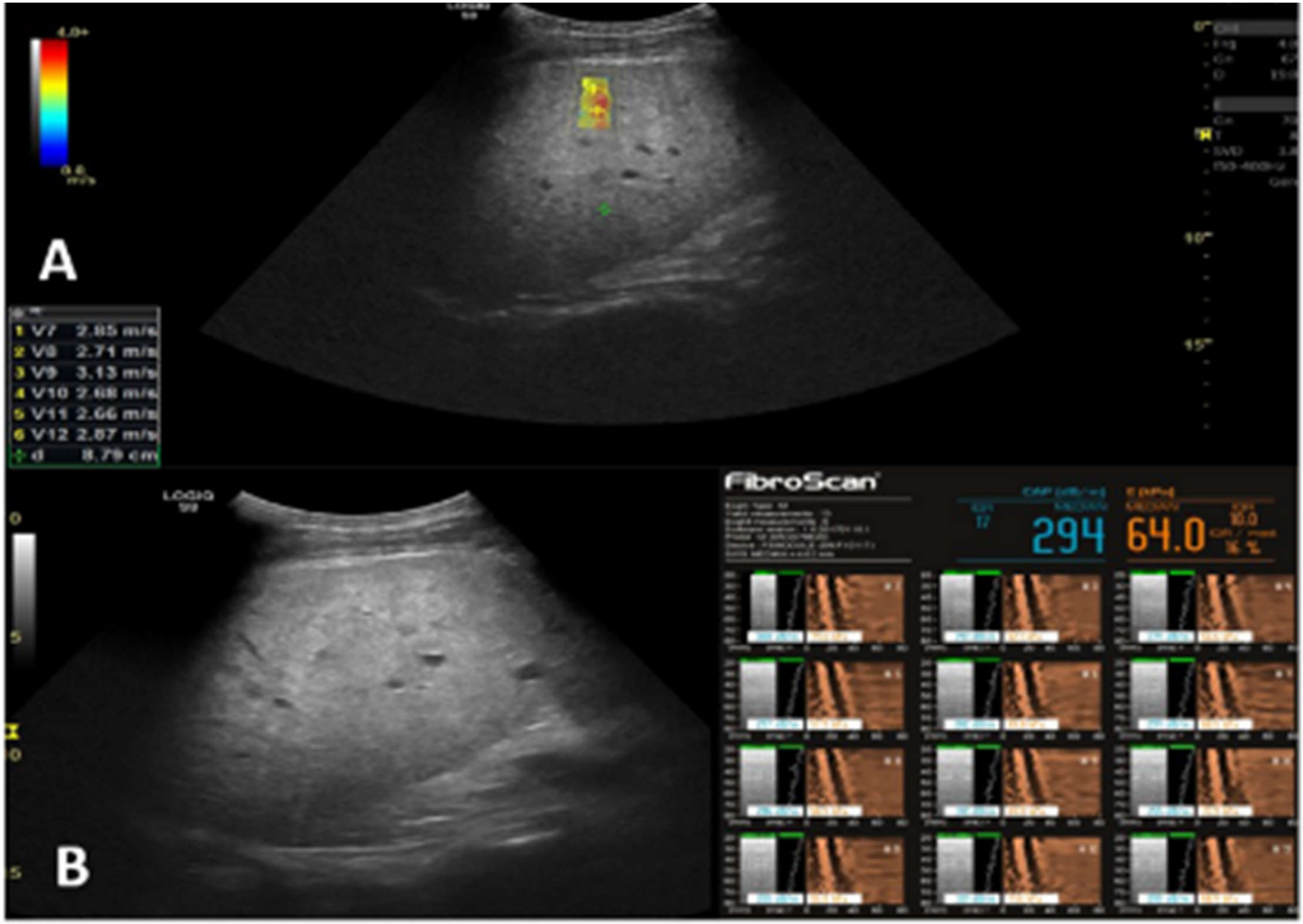
Abstract

Background: The assessment of liver stiffness and the degree of fibrosis are important factors affecting the management strategy. Multiple non-invasive tools are now available to offer an adequate alternative to biopsy. In this study, we tried to compare the performance of 2D shear wave elastography (SWE) to the transient elastography/fibroscan as a non-invasive tool in the prediction of liver stiffness. This is a prospective study of 215 patients confirmed by serology to have positive virus C or B infection. 2D SWE was done followed by vibration-controlled transient elastography (VCTE) known as fibroscan at the same session. Biopsy results were collected.

Results: The mean age was 51.07 years ± 6.07 SD. Five cases were excluded due to insufficient data. Fibroscan failed in 30 cases out of 210 cases (failure rate of 14.3%) compared with only 12 patients (6.7% failure rate) while using SWE. Only 180 patients completed the study to the result analysis. SWE results showed significant agreement to the fibroscan results with 86.7% agreement with a tendency for overestimation of the degree of fibrosis (11.7%). The efficacy of SWE was the highest during the assessment of patients with F0 (98.9%), F1 (97.8%), and F4 (93.3%) respectively and relatively low in F2 (92.8%) and F3 (90.6%).

Conclusion: 2D SWE is a relatively recent non-invasive tool in the assessment of liver fibrosis grading which can be used as an alternative to the fibroscan with almost similar diagnostic performance especially when fibroscan is not capable to obtain adequate results such as in obesity and ascites.

Keywords: Chronic liver disease, Liver stiffness, Shear wave elastography, Fibroscan, Transient elastography



tient 52 years old with chronic hepatitis C infection on follow-up. **a** SWE revealed median velocity = 2.62 m/s and
nt with F4 according to Metavir score. **b** Fibroscan was done for the same patient and revealed kPa = 64 and IQR
4

Screening for Fibrosis Promotes Lifestyle Changes: A Prospective Cohort Study in 4796 Individuals

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BACKGROUND AND AIMS: Early detection of liver fibrosis is believed to promote lifestyle changes. We evaluated self-reported changes in alcohol intake, diet, exercise, and weight after participating in a screening study for liver fibrosis.

METHODS: We conducted a prospective screening study of individuals at risk of alcohol-related liver disease (ALD) or metabolic dysfunction–associated steatotic liver disease (MASLD). We provided lifestyle advice to all participants and evaluated lifestyle changes by questionnaires after 1 week and 6 months, with re-examination of a subgroup after 2 years.

RESULTS: A total of 1850 at risk of ALD and 2946 at risk of MASLD were included, of whom 383 (8%) were screening positive (transient elastography ≥8 kPa). A total of 84% replied to the 6-month questionnaire. In ALD participants, excessive drinking decreased from 46% to 32% after 6

Abbreviations used in this paper: ALD, alcohol-related liver disease;

months. Only 15% reported increased drinking, without differences between screening positive and negative individuals ($P = .698$). In high-risk drinkers, a positive screening test predicted abstinence or decreased alcohol use after 6 months (odds ratio, 2.45; 95% confidence interval, 1.32–4.57; $P = .005$). After 2 years, excessive drinking decreased from 52% to 41% in a subgroup of 752 individuals and a positive screening test predicted abstinence or decreased alcohol use after 2 years (odds ratio, 1.84; 95% confidence interval, 1.09–3.11, $P = .023$). MASLD participants showed similar improvements: 35% improved their diet, 22% exercised more, and 13% reported a weight loss ≥5% after 6 months.

CONCLUSIONS: Screening for liver fibrosis is associated with sustained improvements in alcohol consumption, diet, weight, and exercise in at-risk ALD and MASLD. The changes are most pronounced in screening positive participants but not limited to this group.

Keywords: Lifestyle; Steatosis; Fatty liver disease; Abstinence; Transient elastography

THE END