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RESEARCH LETTER

Obstructive sleep apnoea and non-alcoholic fatty liver disease: Which patients should be referred to hepatologists?

Obstructive sleep apnoea (OSA) is a highly prevalent disease characterized by recurrent episodes of complete or partial upper airway obstruction during sleep, leading to intermittent hypoxia and sleep fragmentation. Most recent estimates of OSA prevalence in adults suggest that 14% of men and 6% of women have clinically significant OSA [1]. There is growing experimental and clinical evidence that OSA and its hypoxia-related consequences may contribute to the development and exacerbation of non-alcoholic fatty liver disease (NAFLD) [2,3]. However, how aggressively clinicians should screen for NAFLD in OSA patients remains a crucial and unresolved question. Identification and quantification of fibrosis is a key issue in patients with NAFLD, as only the stage of fibrosis, but no other histologic features of NAFLD, is independently associated with long-term outcomes [4]. The reference procedure for evaluation of liver fibrosis is histologic examination of a liver biopsy. However, liver biopsy is an invasive procedure and is associated with considerable cost and a significant complication rate of around 1% [5]. Most importantly, in view of the magnitude of the current obesity epidemic and the subsequent number of patients at risk for liver alterations, liver biopsy cannot be considered to be a practical, efficient, and large-scale tool to identify patients at risk of advanced fibrosis. Noninvasive tests have been developed to facilitate evaluation of liver fibrosis, including blood tests and elastography devices [6]. Recent studies have shown a dose-response relationship between OSA severity and non-invasive markers of liver injury, including blood markers and liver stiffness measurement [7,8]. However, these tests are currently available only in specialized centres. Considering the high prevalence of OSA, it would be very useful to have a simple first-line test able to identify patients requiring further specialized liver work-up.

A recent study developed a stepwise algorithm for the identification of patients requiring referral to a hepatologist [9]. The first line of this algorithm uses an easy liver fibrosis test (eLIFT) calculated from routine clinical (age, gender) and laboratory (aspartate aminotransferase, gamma glutamyl transpeptidase, platelets and prothrombin time) parameters. The second line consists of a specialized test combining blood markers of liver fibrosis (FibroMeter, FM) and vibration-controlled transient elastography (VCTE) in a single formula (FM^{VCTE}) [10]. According to the eLIFT-FM^{VCTE} algorithm, patients requiring referral to a hepatologist are identified by eLIFT ≥ 8 then $FM^{VCTE} \geq 0.384$ [9].

We applied the eLIFT-FM^{VCTE} algorithm in 130 patients from the NUMEVOX Cohort [8] with newly diagnosed OSA, at least one criterion for metabolic syndrome (MS), no history of alcohol abuse (daily alcohol intake < 20 g/day in women and < 30 g/day in men), and no other cause of chronic liver disease. The study population, with a mean age of 52.6 ± 8.8 years, consisted of typical mild-to-severe OSA patients (mean apnea-hypopnea index = 31.2 ± 22.3 events per hour of sleep), predominantly male (66.9%), obese or overweight (mean body mass index = 30.3 ± 4.9 kg/m^2), frequently presenting metabolic comorbidities (diabetes, 20.0%; MS, 56.9%). As shown in Fig. 1, 38 of the 130 (29.2%) OSA patients with metabolic comorbidities had a positive first-line liver fibrosis test (eLIFT ≥ 8), and, for 16 of them (42.1%), the second-line specialized test predicted advanced liver fibrosis ($FM^{VCTE} \geq 0.384$). Only 4 (4.5%) of the 92 patients with a negative first-line liver fibrosis test (eLIFT < 8) had suspected advanced liver fibrosis according to the second-line specialized test. Stepwise application of the eLIFT-FM^{VCTE} algorithm showed that an estimated 12.3% of OSA patients with suspected advanced liver fibrosis required referral to a hepatologist.

OSA and MS are frequently associated and share several subclinical metabolic alterations that may contribute to the development and exacerbation of NAFLD, including insulin resistance, oxidative stress, low-grade systemic inflammation and lipolytic fat deposits [2]. An integrated multidisciplinary approach is needed for the management of patients with OSA and metabolic comorbidities, as continuous positive airway pressure therapy, the reference treatment for sleep-disordered breathing, has a limited efficacy on metabolic dysfunction and liver injury [2,3,11]. In this context, a simple first-line test able to identify patients requiring referral for specialized liver work-up would be par-

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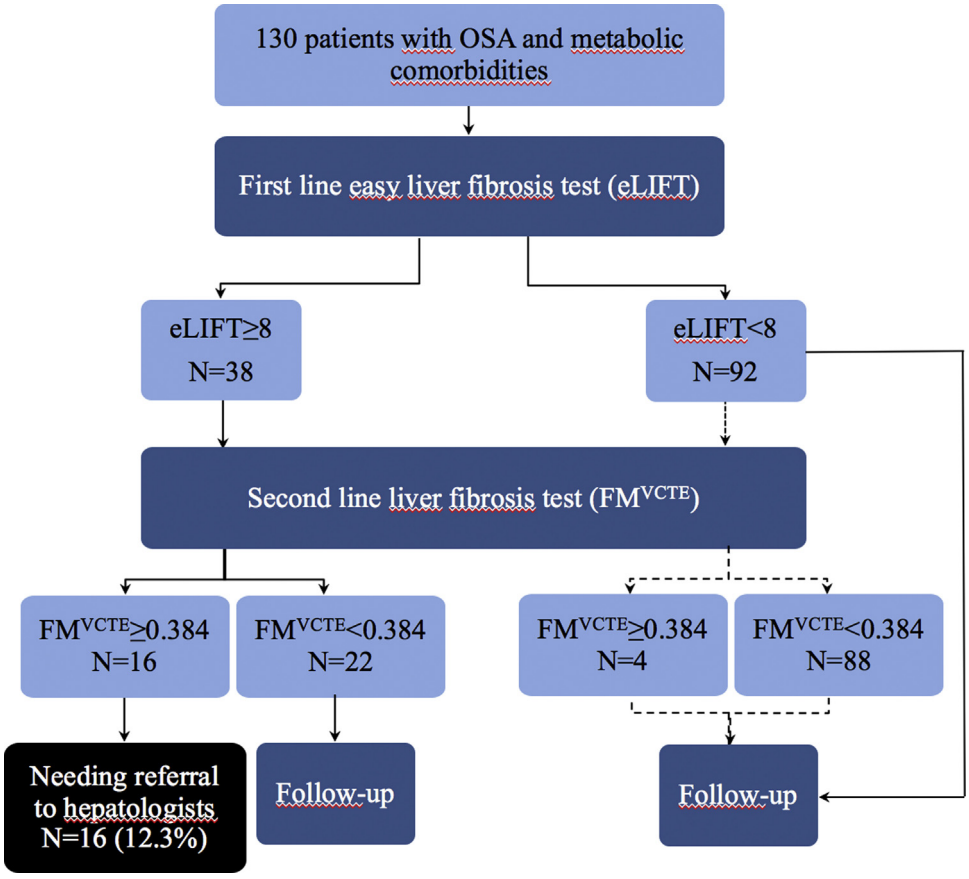

Figure 1 Application of the stepwise eLIFT-FM^{VCTE} algorithm in 130 patients with obstructive sleep apnea (OSA) and metabolic comorbidities for the identification of subjects with suspected advanced liver fibrosis requiring referral to a hepatologist. Abbreviations: eLIFT, easy liver fibrosis test [9]; FMVCTE, combination of blood markers of liver fibrosis FibroMeter, FM and vibration-controlled transient elastography (VCTE) [9].

ticularly useful. Our findings illustrate the potential value of a simple first-line liver fibrosis test usable that can be used by all non-specialized physicians to facilitate liver fibrosis screening in populations at high risk of NAFLD, such as OSA patients with comorbid metabolic disorders. The eLIFT first-line test identified a subset of high-risk patients requiring further assessment, as 42% of patients with eLIFT $\geq$ 8, had FM^{VCTE} $\geq$ 0.384. We acknowledge that liver biopsy was not available in this cohort to evaluate the rate of false-negative and false-positive results. However, FM^{VCTE} has been shown to be the most accurate noninvasive liver fibrosis test in large series of patients with liver biopsy [9,12].

Prospective studies with liver biopsies are required to evaluate the performances of a simple, first-line liver fibrosis test such as eLIFT for liver fibrosis screening in OSA patients. As this test can be easily repeated over time, longitudinal studies are required to determine whether repeating eLIFT during follow-up may help to identify those OSA patients who experience progression of liver fibrosis.

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Disclosure of interest

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