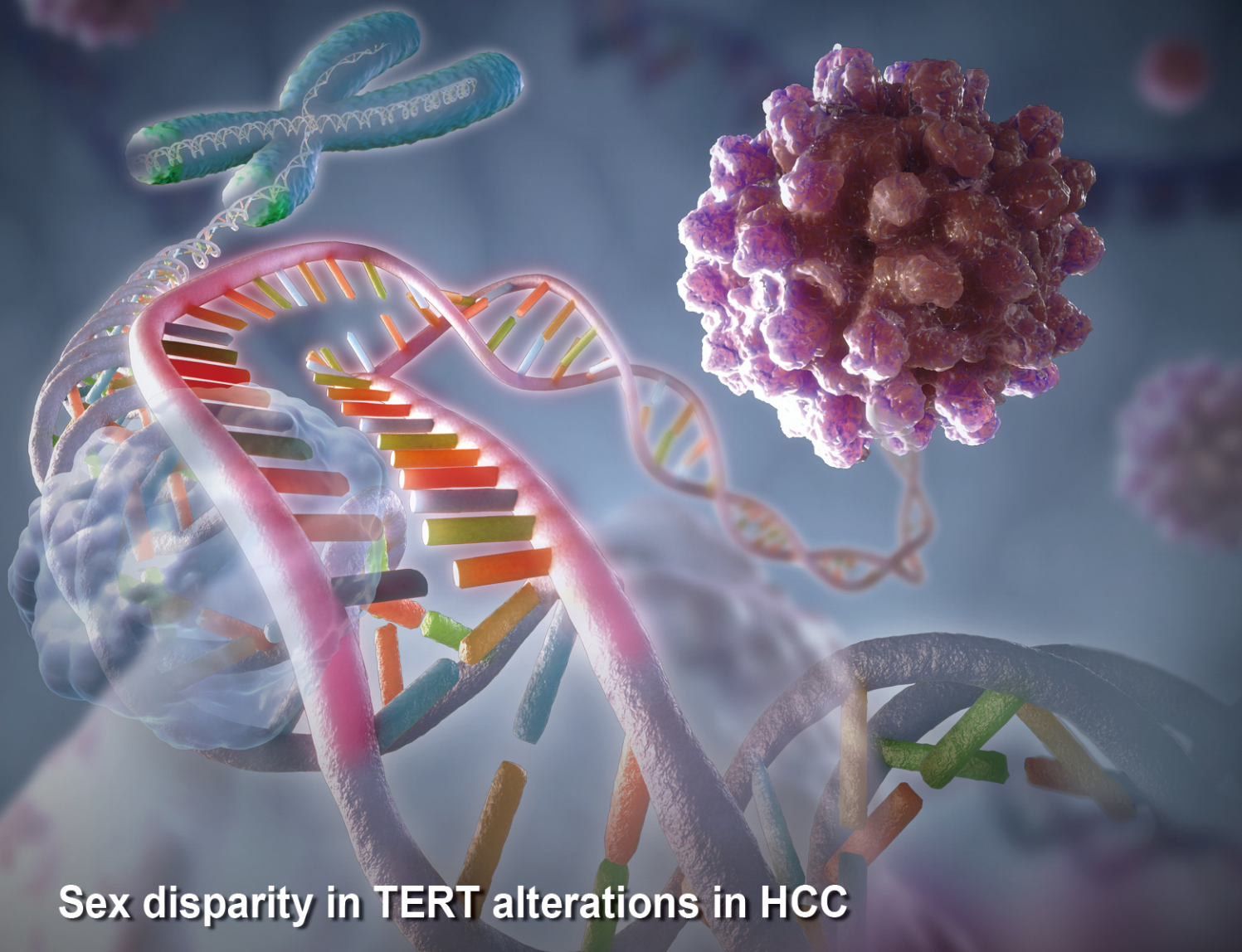


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Molecular characterization of sarcomatoid HCC

Vibration-controlled transient elastography in shaping the epidemiology and management of steatotic liver disease: Editorial on “Current burden of steatotic liver disease and fibrosis among adults in the United States, 2017–2023”

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Steatotic liver disease (SLD) has emerged as a growing concern, closely linked to increased cardiovascular risk and adverse outcomes, with substantial long-term implications for public health.^{1,2} The burden of SLD is likely to persist and grow, driven by the rising prevalence of metabolic risk factors such as obesity and diabetes, especially among adolescents, influenced by lifestyle changes, urbanization, and improved healthcare access.³⁻⁵ The study “Current burden of steatotic liver disease and fibrosis among adults in the United States, 2017–2023” offers an important perspective on the increasing prevalence and

burden of SLD in the US, focusing on metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic dysfunction and alcohol-associated liver disease (MetALD), and alcohol-associated liver disease (ALD).⁶ While previous studies, including those from the Global Burden of Disease (GBD) project, provide valuable global insights into SLD prevalence, their reliance on indirect estimations limits the ability to inform clinical decisions on disease subtypes and fibrosis stages.^{7,8} In contrast, vibration-controlled transient elastography (VCTE) offers direct, non-invasive, and precise measurements, enhancing its role in epidemiological screening.⁹ Beyond screening, VCTE is invaluable for risk stratification, monitoring disease progression, and evaluating treatment efficacy, making it a critical tool in

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both the management and long-term follow-up of patients with SLD (Fig. 1).

VCTE represents a comprehensive advancement in the assessment of SLD, offering a dual capability that significantly enhances disease evaluation.¹⁰ Unlike traditional diagnostic methods, such as liver function tests or the FIB-4 index, which primarily provide indirect estimates of liver function, VCTE directly measures liver stiffness to assess fibrosis severity, while also quantifying liver fat content using the Controlled Attenuation Parameter.¹¹ This combined approach allows for a more complete evaluation of both fibrosis progression and hepatic steatosis, which are two key factors in the pathophysiology of SLD.¹² For instance, the study reports an age-adjusted prevalence of 35.0% for SLD in US adults, while the age-adjusted prevalence was 31.9% for MASLD, 2.2% for MetALD, and 0.8% for ALD.⁶ Using VCTE, the study was able to stratify these patients by fibrosis severity, revealing significant increases in advanced fibrosis among individuals with ALD, where the prevalence of advanced fibrosis was 20.2%, compared to 8.1% in MASLD and 6.3% in MetALD.⁶ This detailed stratification enabled by VCTE provides a clearer picture of liver disease progression, especially when compared to the limitations of traditional diagnostic methods, such as liver function tests or the FIB-4 index. Additionally, the study highlights the COVID-19 pandemic's impact, with SLD prevalence rising to 9.8% during 2021–2023, compared to 7.4% pre-COVID-19 ($P=0.039$). This underscores VCTE's role in tracking steatosis changes linked to pandemic-related lifestyle disruptions, like increased alcohol use and inactivity. Real-time monitoring of such changes enables more timely and targeted interventions.

VCTE offers a key advantage in providing continuous monitoring and long-term usability.¹³ While liver biopsy is traditionally regarded as the gold standard in clinical trials and research, its application to larger populations is limited by significant challenges. This issue is particularly pronounced in chronic conditions such as SLD, where clinical events unfold over extended periods with relatively low incidence rates. Consequently, effective assessment of clinical outcomes or the evaluation of drug efficacy and safety

in SLD requires large sample sizes and repeated monitoring of fibrosis and steatosis over time—capabilities that VCTE, with its non-invasive, reliable, and longitudinal monitoring approach, can provide. Furthermore, in the context of long-term follow-up, the often subtle and insidious progression of fibrosis and steatosis introduces additional complexities in disease management, further underscoring the necessity for non-invasive, convenient monitoring tools like VCTE. A study on MASLD highlighted the prognostic significance of VCTE-based scores, such as Agile 3⁺ and Agile 4, which evaluate advanced fibrosis and cirrhosis.¹⁴ The findings indicated that both baseline and serial VCTE measurements demonstrated high accuracy in predicting liver-related events, including hepatocellular carcinoma and hepatic decompensation. Furthermore, the ability to monitor changes in Agile scores over time offered valuable insights into the progression of liver disease. Patients whose scores deteriorated exhibited a greater risk of liver-related complications. This emphasizes the importance of VCTE for long-term monitoring, allowing clinicians to make timely adjustments to treatment plans based on real-time data. A recent study examining patients with MASLD investigated the role of VCTE in assessing the efficacy of pharmacological treatments.¹⁵ The findings indicated that serial VCTE measurements facilitated the monitoring of liver stiffness progression and liver fat content in patients undergoing statin therapy. This treatment was linked to a decreased rate of liver stiffness progression and a lower risk of liver-related complications. The capability of VCTE to capture dynamic changes in liver stiffness and fat content over time provided clinicians with valuable real-time data, enabling them to evaluate the long-term effects of treatment. This highlights how serial VCTE assessments can be instrumental in monitoring treatment outcomes, serving as a vital tool for gauging the effectiveness of interventions and for making necessary adjustments to treatment plans.

This study's strength lies in its detailed breakdown of SLD into distinct subtypes—MASLD, MetALD, and ALD—each with unique underlying mechanisms, requiring tailored monitoring and intervention strategies.¹⁶ VCTE plays a pivotal role in the personalized management of these

Abbreviations:

ALD, alcohol-associated liver disease; GBD, Global Burden of Disease; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic dysfunction and alcohol-associated liver disease; SLD, steatotic liver disease; VCTE, vibration-controlled transient elastography

subtypes, addressing the silent progression of liver damage and offering precise, non-invasive tracking of fibrosis and fat content.¹⁷ In MASLD, which is primarily driven by insulin resistance and metabolic syndrome, liver damage typically progresses slowly without clear symptoms, making early detection challenging. However, MASLD is also closely associated with increased cardiovascular risk, with metabolic syndrome and insulin resistance serving as common pathways linking liver damage and cardiovascular complications.¹⁸ These dual risks highlight the importance of early detection and intervention to manage both liver-related and cardiovascular outcomes. VCTE overcomes this challenge by enabling non-invasive tracking of both fibrosis severity and fat content, facilitating the identification of clinically undetectable fibrosis stages. This capability, combined with the growing number of prognostic models that integrate VCTE, enhances the early monitoring and management of MASLD. Serial VCTE measurements are essential for monitoring disease progression and evaluating the effectiveness of interventions such as lifestyle modifications and pharmacological treatments before the disease advances to later stages. Additionally, the ability of VCTE to monitor changes in liver stiffness and fat content may offer indirect insights into cardiovascular risk reduction, as

improving metabolic parameters in MASLD could lower the risk of cardiovascular events.¹⁹ For ALD, where alcohol cessation is the primary therapeutic approach, the need for frequent VCTE monitoring is more pronounced due to the significant impact of alcohol consumption on liver damage progression. Unlike MASLD, the development of clinical prognostic models that integrate VCTE in ALD patients is still limited, and more clinical research is required to explore how VCTE, combined with key features such as alcohol consumption data and alcohol consumption biomarkers, can enhance the accuracy of such models. MetALD, a newly defined subtype that combines metabolic and alcohol-related factors, presents a more complex disease trajectory. Although this subtype is relatively underexplored, it has gained increasing clinical relevance, with evidence suggesting more rapid fibrosis progression compared to MASLD. VCTE offers valuable longitudinal data that helps track both fibrosis progression and fat content, providing essential insights for clinicians managing patients with MetALD. Given the increasing recognition of MetALD as a significant clinical condition and the growing body of research in this area, further studies are needed to better understand the role of VCTE in its management, including epidemiological research, the development of prognostic mod-

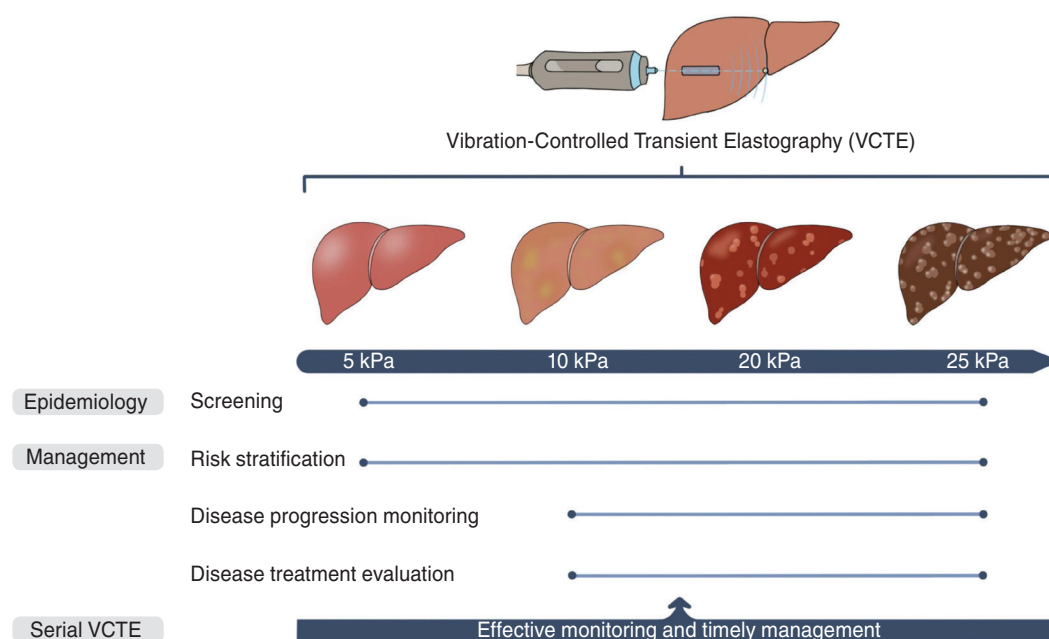


Figure 1. Vibration-controlled transient elastography for screening, risk stratification, disease progression monitoring, and drug treatment evaluation in steatotic liver disease.

els, and its application in treatment strategies.

While VCTE has demonstrated significant advantages in assessing liver stiffness, its widespread adoption faces several challenges. The high equipment cost and the need for specialized training to obtain reliable measurements are major barriers, particularly in low-resource settings. These issues are further compounded in areas with a high prevalence of obesity, where obtaining accurate measurements is more difficult. Moreover, accessibility remains a significant issue in medically underserved regions or areas where primary care doctors have insufficient awareness of VCTE's benefits, limiting its broader application and potential impact. Another important limitation is the reproducibility and repeatability of VCTE measurements, with variability coefficients reaching up to 35.6% between operators and across different days.²⁰ However, this challenge can be mitigated by performing repeated measurements, which are both feasible and straightforward with VCTE. To fully realize VCTE's potential in clinical practice and epidemiological research, it is essential to address these barriers by reducing costs, improving accessibility, providing adequate training, and leveraging repeated measurements to enhance reliability.

VCTE has emerged as a critical tool in screening and management of SLD. Its ability to comprehensively assess both fibrosis severity and liver fat content facilitates precise and comprehensive risk stratification. Furthermore, VCTE's dynamic, real-time monitoring of disease progression addresses the challenges inherent in tracking the gradual evolution of SLD and provides robust fibrosis evaluation for large-scale clinical populations. With ongoing advancements in both research and technology, VCTE is poised to further strengthen its contribution to personalized treatment strategies and large-scale epidemiological investigations.

Authors' contribution

X-D Zhou and M-H Zheng contributed to the conceptualization, and writing of the manuscript. X-D Zhou, TC Yip, DQ Huang, MD Muthiah, M Nouredin, and M-H Zheng critically reviewed the manuscript for important intellectual content. All authors reviewed and approved the submission.

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Conflicts of Interest

Terry Cheuk-Fung Yip: Serves as a speaker and consultant for Gilead Sciences. Daniel Q. Huang: Serves on the advisory board for Gilead Sciences and Roche. Mark Dhinesh Muthiah: Serves as a consultant for Roche, Astellas, and Gilead; as an advisory board member for Lerna-Bio; and has received honoraria for paid speaking engagements from Boston Scientific, Olympus Medical, Roche, Astellas, and Perspectum. He is supported by the Singapore Ministry of Health through the National Medical Research Council (NMRC) Office and MOH Holdings Pte Ltd under the NMRC Clinician Scientist-Individual Research Grant (MOH-001228) and Clinician Scientist Award (MOH-001631), as well as the National Research Foundation, Singapore (NRF) under the NMRC Open Fund – Large Collaborative Grant (MOH-001325), administered by the NMRC Office, MOH Holdings Pte Ltd. Ming-Hua Zheng: Serves as a speaker for AstraZeneca, Hisky Medical Technologies, and Novo Nordisk; as a consultant for Boehringer Ingelheim and Eieling Technology; and has received consulting fees from Boehringer Ingelheim.

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