ISSN 2308-3840 (online)

World Journal of *Meta-Analysis*

World J Meta-Anal 2023 December 18; 11(7): 313-379

Published by Baishideng Publishing Group Inc

World Journal of Meta-Analysis

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World Journal of Meta-Analysis

Quarterly Volume 11 Number 7 December 18, 2023

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NAME OF JOURNAL

World Journal of Meta-Analysis

ISSN

ISSN 2308-3840 (online)

LAUNCH DATE

May 26, 2013

FREQUENCY

Quarterly

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PUBLICATION DATE

December 18, 2023

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https://www.wjgnet.com/bpg/gerinfo/242

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https://www.wjgnet.com/bpg/GerInfo/239

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https://www.f6publishing.com

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World Journal of Meta-Analysis

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World J Meta-Anal 2023 December 18; 11(7): 340-350

DOI: 10.13105/wjma.v11.i7.340

ISSN 2308-3840 (online)

MINIREVIEWS

Transient elastography (FibroScan) in critical care: Applications and limitations

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Specialty type: Medicine, research and experimental

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Ferraioli G, Italy; Manesis EK, Greece

Received: July 28, 2023
Peer-review started: July 28, 2023
First decision: August 10, 2023
Revised: August 28, 2023
Accepted: September 22, 2023
Article in press: September 22, 2023
Published online: December 18, 2023

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Abstract

FibroScan® is a non-invasive device that assesses the 'hardness' (or stiffness) of the liver *via* the technique of transient elastography. Because fibrous tissue is harder than normal liver, the degree of hepatic fibrosis can be inferred from the liver hardness. This technique is increasingly being employed to diagnose liver fibrosis, even in critically ill patients. It is now being used not only for diagnosis and staging of liver cirrhosis, but also for outcome prognostication. However, the presence of several confounding factors, especially in critically ill patients, may make interpretation of these results unreliable. Through this review we aim to describe the indications and pitfalls of employing FibroScan in patients admitted to intensive care units.

Key Words: FibroScan; Intensive care unit; Liver dysfunction; Liver stiffness; Transient elastography

Core Tip: Liver dysfunction is common in critically ill patients. For diagnosis, severity assessment, and prognostication of liver fibrosis, liver biopsy is considered the gold standard. However, because of inherent risks associated with the invasive nature of liver biopsy, non-invasive tests may be preferable in intensive care unit patients. Serology markers for liver fibrosis lack specificity and accuracy and hence newer tests like liver stiffness measurement (LSM) are increasingly been used in these patients. Transient elastography using FibroScan is arguably the most commonly employed and validated tool for LSM. FibroScan has been used in the management, prediction of complications, and prognostication of various liver diseases including acute and chronic conditions. However, there are several integral limitations which should be considered while applying this test in critically ill patients.

Citation: Kataria S, Juneja D, Singh O. Transient elastography (FibroScan) in critical care: Applications and limitations. *World J Meta-Anal* 2023; 11(7): 340-350
URL: https://www.wjgnet.com/2308-3840/full/v11/i7/340.htm
DOI: https://dx.doi.org/10.13105/wjma.v11.i7.340

INTRODUCTION

Hepatic dysfunction is quite prevalent in critically ill patients, especially among those with multiple organ failure, with a reported incidence of 10%-40%[1,2]. Notably, hepatic dysfunction is linked to a higher mortality rate in critically ill patients, even without pre-existing liver disease. Indeed, the hepatic function is frequently used in clinical multifactorial scoring systems for prognostication in the intensive care unit (ICU) setting, for instance, Acute Physiology and Chronic Health Evaluation II (cirrhosis as an element) or the Sequential Organ Failure Assessment score (serum bilirubin and international normalized ratio as variables)[3]. Still, liver dysfunction and the role of the liver in the pathogenesis of systemic inflammatory response syndrome, sepsis, and multiorgan failure in critically ill patients may be underrated because they are less obvious and less immediately life-threatening compared to respiratory, cardiovascular, or renal dysfunction. Since no single physiologic variable allows for early detection of hepatic dysfunction, current diagnostic criteria are based on laboratory tests, mostly serum bilirubin levels or international normalized ratio. Only a few specialized centers offer sophisticated measurements like the indocyanine green plasma disappearance rate, which reflects liver perfusion and function in critically ill patients[4]. Among other non-invasive tests, the measurement of liver stiffness (LS) by transient elastography (TE) is increasingly used to evaluate hepatic dysfunction in critically ill patients. TE correlates well with liver dysfunction, and increasing stiffness values are also related to increased mortality in the ICU and non-hepatic organ failure patients[5]. Additionally, TE has shown promise in predicting the development of complications such as hepatic encephalopathy and hepatorenal syndrome in critically ill patients[6]. As a non-invasive test, TE can provide valuable information for monitoring liver function in critically ill patients, allowing for early detection and implementing appropriate interventions to prevent further deterioration of liver function and improve patient outcomes. However, even these non-invasive tests are not ideal and are associated with their limitations; hence, it becomes imperative for the practising physician to be aware of any existing limitations before applying and interpreting such tests.

LS MEASUREMENT

Non-invasive tests to evaluate liver fibrosis may be broadly categorised as blood-based tests, tests assessing physical properties of liver tissue, and imaging modalities (Table 1). Serum markers for detecting liver fibrosis are non-specific and have a poor accuracy[7]. Hence, other non-invasive tests, including LS measurement (LSM) and radiological imaging, are generally preferred. LSM can be performed using techniques based on magnetic resonance or ultrasonography. Ultrasound-based elastographic methods have been further classified as per the guidelines by the European Federation of Societies of Ultrasound in Medicine and Biology (Figure 1)[8-10]. Even though LSM using techniques like Acoustic Radiation Force Impulse Elastography with or without the Aixplorer® system (SuperSonic Imagine, France) offers the advantage of providing ultrasound images, FibroScan remains the most widely used and validated tool[7]. TE has been used not only in the management of patients with chronic liver disease but also in acute liver failure (ALF) and those without any underlying liver disease (Table 2).

FIBROSCAN IN PATIENTS WITHOUT PREEXISTING CHRONIC LIVER DISEASE

Acute liver dysfunction in critically ill patients

Hepatic function is often impaired in critically ill patients for several reasons, such as endotoxemia, changes in circulation (cardiac failure), and external factors (such as increased intraabdominal or intrathoracic pressure due to an impending abdominal compartment or mechanical ventilation, respectively). Hypoxic hepatitis occurs with an incidence of 10% in critically ill patients and is associated with an in-hospital mortality rate of 50%[11]. Pro-fibrogenic cells like hepatic stellate cells (HSCs) and myofibroblasts are quickly activated to make extracellular matrix components and hyaluronic

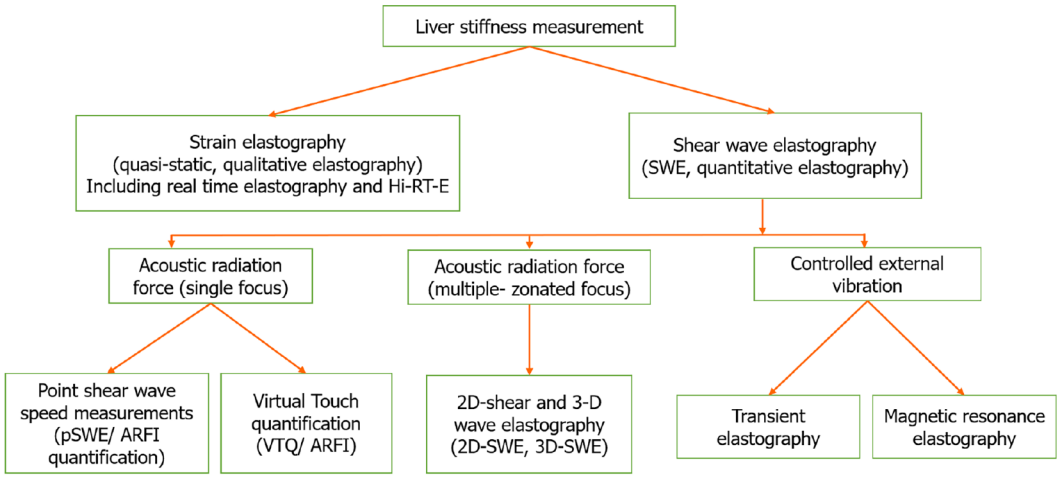
Table 1 Non-invasive tests for diagnosing and staging of liver fibrosis

Categories of test	Clinical application	Clinical tests
Blood-based tests	Serum markers of fibrosis, laboratory variables	Alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transferase, platelets, albumin
Methods assessing physical properties of the liver tissue	Liver stiffness	Transient elastography, bidimensional shear wave elastography, magnetic resonance elastography
Imaging methods	Assessing the anatomy of the liver and other abdominal organs	Ultrasound, CT scan, magnetic resonance scans

CT: Computed tomography.

Table 2 Potential clinical applications of transient elastography

	Clinical condition	Clinical applications
Patients without chronic liver disease	Acute liver dysfunction	Diagnosis. Prognostication
	Heart failure	Response to therapy. Prognostication. Prediction of complications like cardiac cirrhosis
	Left ventricular assist device placement	Prognostication. Therapeutic intervention. Prediction of complications like right ventricular failure
	General critically ill	Prognostication marker
	Pregnancy	Prediction of complications like preeclampsia
	Acute liver failure	Differentiate between acute and chronic liver dysfunction. Prognostication. Need for transplantation
Patients with underlying chronic liver disease	Chronic liver failure	Diagnosis of decompensation. Differentiation of aetiology. Severity assessment. Prediction of complications like portal hypertension, variceal bleeding, hepatocellular carcinoma. Response to treatment. Prognostication
	Post liver transplant	Prognostication. Acute transplant rejection



DOI: 10.13105/wjma.v11.i7.340

Figure 1 Classification of ultrasound based elastographic techniques. SWE: Shear wave elastography; pSWE: Point shear wave elastography; APFI: Adolescents' Psychosocial Functioning Inventory; VTQ: Virtual touch quantification.

acid, an indirect sign of collagen formation in the liver. The combination of hepatocyte oedema, bilirubin elevation, and intrahepatic collagen deposition can increase LS. Koch *et al*[12] examined critically ill patients in a medical ICU to assess LS and its clinical impact and predictive power to predict mortality. They measured LS at admission, day 3, day 7, and weekly during the ICU course in critically ill medical patients. ICU patients had a significantly higher LS than standard care patients without liver disease. ICU patients without cirrhosis had median LS values of about 10 kPa, indicative of severe hepatic fibrosis in the general population. Values > 12.5 kPa, which generally indicate established liver cirrhosis, were present in 33% of medical, non-cirrhotic ICU patients at admission. At admission, septic and non-septic patients had similar LS. However, in an extensive subgroup analysis, abdominal sepsis patients had a higher LS than pulmonary

sepsis patients. At admission, septic and non-septic patients had similar LS. However, in an extensive subgroup analysis, abdominal sepsis patients had a higher LS than pulmonary sepsis patients[12].

LSM reflects liver function upon admission to the ICU. On days 3 and 7, LS correlated with kidney, lung, and heart/circulation biomarkers but not with liver biomarkers. High-volume fluid resuscitation, vasopressors, and organ support therapies like mechanical ventilation and continuous veno-venous hemofiltration may change the significance of elevated LS in medical ICU patients, indicating non-hepatic organ failure in follow-up examinations. Also, patients with LS values greater than or equal to 18 kPa had substantially reduced survival rates during ICU treatment and long-term observation [12]. Despite this, there is a dearth of information on TE's ability to predict "challenging end-points" like mortality.

Heart failure

Heart failure (HF) is a complex disease associated with multisystem organ failure and recurrent hospital admission, with 30%-45% of patients hospitalized with acute decompensated HF (ADHF) dying within one year[13]. Congestive hepatopathy (CH) is caused by protracted passive venous congestion as the elevated central venous pressure (CVP) in right-sided HF (RHF) is transmitted to the hepatic veins. ADHF further increases CVP with a resultant increase in hepatic congestion, and this relationship may have prognostic significance[14]. Right heart catheterization (RHC), though a gold standard method, is invasive and costly for assessments in RHF patients, necessitating the search for an accurate, non-invasive test. In HF, increased LS may reflect residual congestion secondary to volume, pressure overload, and/or inadequate liver perfusion with low cardiac output in patients hospitalized with ADHF. LS is reversibly associated with CVP with a direct relationship, increases exponentially with cardiac functional deterioration, and improves dramatically after diuretic therapy (decongestion)[15].

A study that compared LS in people with normal cardiac function, stable left HF (LHF), stable RHF, and ADHF showed that all of the HF groups had a significantly higher LS than the control group. Furthermore, the ADHF group demonstrated notably higher right atrial pressure and LS than the stable LHF group, with a median of 11.2 kPa *vs* 4.7 kPa, respectively (P = 0.01)[16]. Hopper *et al*[17] conducted a cross-sectional investigation whereby they observed a positive correlation between LSM and increased levels of bilirubin, gamma-glutamyl transferase, and alkaline phosphatase in both HF and ADHF groups. Throughout the clinical progression of CH, liver indicators exhibit fluctuations and are generally considered unreliable, even in the presence of substantial changes in body volume. This observation further reinforces that LSM is a more advantageous and superior diagnostic tool in this context. The use of LS may be particularly beneficial when the hemodynamic status cannot be readily assessed at the bedside on physical examination, and the assessment of LS by TE is rapid, simple, and objective. Recent studies have shown that RHC and LSM have a baseline correlation[18].

Additionally, insufficient alleviation of congestion at discharge for ADHF is linked to higher morbidity and mortality. Despite this, a lack of an objective assessment of HF results in the discharge of many patients with residual congestion. Compared to other non-invasive markers for HF, LSM may exhibit more accuracy in illustrating the decongestion process. In a study conducted by Yoshitani *et al*[19], total serum bilirubin, aspartate aminotransferase, alanine transaminase, and gamma-glutamyl transferase were measured before and after diuresis. The results indicated that there was no statistically significant change in these parameters. However, it was seen that body weight, LSM, and brain natriuretic peptide (BNP) all exhibited a substantial drop.

The median LSM at admission was utilized by Saito *et al*[20] to classify patients with ADHF into low LSM (8.8 kPa) and high LSM (8.8 kPa) groups, with mortality, cardiovascular disease, and readmission rates serving as primary outcomes. After a median follow-up period of 153 d, it was observed that the group with high LSM had significantly higher rates of composite events (P = 0.001) and readmission rates (P = 0.022). The only independent risk factor for cardiac events was a high LSM level, not echocardiographic or serologic data. Soloveva *et al*[21] assessed FibroScan-based LSM in patients with HF both during admission and prior to discharge. Their findings revealed a statistically significant increase in the likelihood of unfavorable outcomes when LSM exceeded 13 kPa upon admission and reached or exceeded 5 kPa at the time of discharge. Discharge LSM predicted HF readmission independently and was associated with worse composite endpoints and overall mortality. A recent meta-analysis also suggested that LS may be a novel, independent prognostic marker of cardiovascular outcomes in patients hospitalized with ADHF when assessed without liver disease, supporting LSM as a clinically relevant tool to assess adequate decongestion before discharge. Further, measuring LS may help identify patients at risk of developing cardiac cirrhosis due to HF, as higher systemic venous pressure is well-recognized as a significant risk factor for cardiac cirrhosis. The possibility of cardiac cirrhosis can be excluded if there is complete normalization of LS following the removal of fluid retention. Thus, LS could be a helpful non-invasive surrogate marker for hydrostatic pressure to offer additional prognostic information in patients hospitalized with ADHF and a guiding tool for optimal therapy during ADHF (Table 3).

Left ventricular assist device placement

Left ventricular assist devices (LVADs) are increasingly becoming a common therapy for managing advanced cardiac failure. Secondary right ventricular (RV) failure in LVAD occurs in 5%-44% of patients. The observed phenomenon can be related to the compromised ability of the right heart to adequately manage an increased output from the left side of the heart, resulting in an exaggerated leftward displacement of the interventricular septum and a deterioration in the hemodynamic conditions, leading to the exacerbation of tricuspid regurgitation. This condition generally manifests during a 2-wk period following LVAD insertion and is correlated with increased ICU needs and an unfavorable prognosis. No singular marker or risk algorithm possesses substantial predictive value for problems following LVAD implantation. Nevertheless, other tests, including BNP, CVP, pulmonary artery pulsatility index, RV stroke work index, and the ratio of CVP to pulmonary capillary wedge pressure, are frequently employed to assess the necessity of implanting a RV assist device (RVAD) and performing tricuspid valve replacement prior to surgery.

Table 3 Liver stiffness measurement in heart failure

	Measurement
Indications of FibroScan in HF	(1) Assessment of adequate venous decongestion prior to discharge; (2) prognosis after an acute exacerbation; and (3) risk stratification for determining right ventricular support needs before LVAD placement
The cut-off value of LS in HF	LS < 7 kPa: Normal RV filling pressure and exclusion of RV failure
	LS 7-8 kPa: Gray zone
	LS 8-12.5 kPa: Increased risk of morbidity and mortality from HF or cardiac death; increased risk of RV failure in case of LVAD implantation
	LS > 35 kPa: BiVAD needed due to RV failure

HF: Heart failure; LS: Liver stiffness; LVAD: Left ventricular assist device; BiVAD: BiVACOR biventricular assist device; RV: Right ventricular.

Nishi *et al*[22], using FibroScan to evaluate LVAD candidates, observed that LSM was substantially higher in patients needing RVAD. Based on the receiver operator characteristic analysis, a cut-off of 7.0 kPa was determined for the increased RVAD requirement. Significantly higher LSM was seen in patients who experienced major adverse events (MAEs) than those who did not (22.4 ± 17.4 *vs* 8.0 ± 5 kPa, $P < 0.05$). MAEs were significantly higher in individuals with LSM ≥ 12.5 kPa, with 80% of these patients experiencing MAEs compared to just 25% of patients with LSM less than 12.5 kPa. Various indicators of HF were assessed in this study, such as pre-operative haemodynamic assessments, BNP, and transaminases. However, LSM was the sole risk factor found to be independently associated with MAEs. Although this does not rule out the possibility that liver fibrosis will affect LSM, it does highlight the predictive power of elastography as a separate risk factor for unfavorable events after LVAD implantation and as a tool to supplement current predictors of unfavorable outcomes.

In a study by Kashiyama *et al*[23], the authors examined the LS following LVAD implantation. The results revealed a significant elevation in LS levels among patients experiencing RV failure subsequent to LVAD implantation compared to those without RV failure. Serial measures of LS might provide valuable insights into the perioperative optimization of right-sided filling pressure, even without needing a pulmonary catheter study. This is because LS is known to be immediately influenced by fluctuations in CVP. It is important to mention that cases demonstrating higher LS values, exceeding the expected values based on pre-operative CVP, had a higher probability of experiencing RV failure (RVF) or requiring the insertion of an RVAD following the implantation of a LVAD. This suggests that LSM may serve as an indicator not only of CVP but also of other parameters, such as RVF or RV compliance. In patients with an increased LS, an increased preload might have a more adverse effect on the right ventricle than the advantageous effect of decreased afterload with LVAD support. This observation suggests that a right ventricle with decreased compliance can rapidly elevate RV filling pressure by augmented preload through increased LVAD flow.

General critical care

The most important clinical endpoint for critically ill ICU patients is overall survival. Lindvig *et al*[24] conducted a study in the emergency room to assess initial LSM by elastography to predict 30-d mortality. Increased LS, defined as > 8 kPa, was detected in 22.6% (48/213) of patients. The 30-d mortality rate for patients with TE values > 8 kPa was 20.8%, as opposed to 3.7% for patients with an LS ≤ 8 kPa. Furthermore, it was shown that LS greater than 8 kPa served as a significant independent prognostic factor for mortality. In a separate study, LS was evaluated in a cohort of 108 critically ill patients. LS was measured at admission, day 3, day 7, and weekly during their ICU stay. They noted a substantial increase in LS among critically ill individuals compared to standard-care patients who were matched for sex and age (n = 25). Patients without cirrhosis with LS values greater than 18 kPa upon admission to the ICU exhibited higher death rates in both the ICU and the long term. In a recent meta-analysis by Wang *et al*[25], the relative risk for all-cause mortality was 4.15 for patients with a high LS, which increased by 1.06 for each unit increment of LS. Intriguingly, LS appeared to predict all-cause mortality regardless of the aetiology.

Pregnancy

Twenty-five percent of pregnant women experience an increase in LS, which occurs almost exclusively in the third trimester and quickly returns to normal within a day after giving birth. However, the cause of the increase in LS remains unknown. Since liver inflammation or apoptosis often takes more than a day to resolve, the sudden drop in LS following delivery suggests a mechanical source, such as hemodynamic alterations, including inferior vena compression. Hormonal changes, a rise in the volume of blood, and modifications to the liver's functioning are a few more possibilities for LS elevation during pregnancy[26]. To completely comprehend the underlying mechanisms, more studies are required. Therefore, increased LS during pregnancy should not be confused with liver fibrosis or illness.

On the other hand, LS has a strong correlation with pregnancy-related problems like preeclampsia. A German study looked at two categories of complications: Preeclampsia (n = 22) and intrahepatic cholestasis of pregnancy (ICP) (n = 40). The mean LS values for preeclampsia and ICP were found to be 17.9 kPa and 6.9 kPa, respectively [area under the receiver operating characteristic (AUROC) = 0.82], with both groups showing elevated LS compared to healthy pregnancies in the third trimester. LS and leucocytes were separate predictors of preeclampsia in the multivariate model. Preeclampsia was twice as likely to develop in women with LSM greater than 8 kPa[27]. These findings suggest that LSM

could potentially serve as a valuable biomarker for predicting the development of preeclampsia during pregnancy. Nevertheless, further research is needed to validate these results and determine the underlying mechanisms linking LS to preeclampsia. Additionally, understanding how LS is associated with preeclampsia could provide valuable insights into the pathophysiology of this condition and potentially lead to new therapeutic approaches.

ALF

ALF is a life-threatening clinical illness with a high mortality rate if prompt and advanced intensive care or liver transplantation (LT) is not administered. In the early stages of ALF, accurate mortality prediction continues to pose challenges. The scoring systems of Clichy and King's College are widely acknowledged in the medical field as effective tools for predicting mortality in patients with ALF. However, it is imperative to continue making advancements, as the prognosis is contingent upon a prompt and suitable beginning of treatment. The inclusion of a liver biopsy should be consistently contemplated in individuals presenting with ALF to promptly validate the diagnosis or assess the concentrations of iron or copper. Nevertheless, the diminished coagulation factors resulting from liver failure might provide a constraint for performing biopsies, necessitating reliance only on transjugular alternatives in such circumstances. Therefore, it is imperative to develop alternative approaches for predicting the probability of spontaneous remission or the requirement for LT.

LS elevation in the context of ALF is believed to be attributed to hepatic edema, inflammatory infiltration, and tissue necrosis rather than fibrosis. Nevertheless, HSCs differentiate into contractile myofibroblasts, leading to tissue repair alongside cellular collapse and fibrosis[28]. Dechêne *et al*[29] showed that fibrogenesis is a component of ALF at various stages and can potentially contribute to elevated LS. Fibrosis may potentially work as a mechanism for wound healing, temporarily preserving the structural integrity of the organ until functioning hepatocytes and accessory cells can replace the damaged tissue regions. The resolution of fibrosis is associated with the programmed cell death of activated HSCs. In individuals with short-term liver impairment, such as from poisoning or mycotoxicosis, LS may be decreased. Conversely, LS exhibited an elevation among those experiencing persistent liver damage, such as those afflicted with viral hepatitis. The measurement of LS in individuals diagnosed with ALF can serve as a reliable and timely biomarker for identifying fulminant hepatitis in conjunction with evaluating bilirubin levels, prothrombin time, and platelet count. It correlates with alanine aminotransferase and total bilirubin in acute hepatitis[30]. It is further proposed that a more accurate prognosis assessment can be attained by assessing LS at two distinct time intervals, such as days 0 and 7, following admission to the hospital. This might potentially serve as a tool for prognostic estimation. However, further research is required in order to determine an appropriate threshold for stiffness.

FIBROSCAN IN PATIENTS WITH CHRONIC LIVER DISEASE

Chronic liver disease

Hepatic decompensation: Cirrhosis of the liver is one of the primary causes of death globally. It is characterized by two clinically distinctive conditions: Compensated and decompensated cirrhosis. Decompensation refers to the emergence of pronounced clinical manifestations, such as ascites, haemorrhage, hepatic encephalopathy, hepatorenal syndrome, or jaundice, which are indicative of an unfavorable prognosis.

Therapy aims to prevent clinical decompensation, which has a much worse prognosis than compensated liver cirrhosis. The hepatic venous pressure gradient (HVPG), which is the difference between the pressure in the "wedged" or "occluded" hepatic vein and the pressure in the "free" hepatic vein, is believed to be the most accurate method for measuring the presence and severity of portal hypertension (PH), except in cases such as HF in which HVPG and portal pressure can be different. This technique is relatively costly and unavailable at the bedside and in non-specialized institutions, requires appropriately trained personnel, and may be associated with procedural complications. There is a remarkable correlation between the HVPG and LS below 10 mmHg, with the latter being a reproducible and easy-to-perform non-invasive assay for assessing PH. For HVPG > 10 mmHg, the cut-off of 21 kPa for LSM demonstrated a high specificity (over 90%)[31]. However, the reference standard and LSM relationship diverge for larger values. In addition to the structure-dependent component of LS caused by liver fibrosis, the pressure balance between inflow and outflow from the hepatic sinusoidal system influences LSM, giving it a dynamic element. The 2015 Baveno VI consensus recommended using LS > 20-25 kPa to detect clinically significant PH (CSPH) in untreated hepatitis C or hepatitis B virus-related compensated advanced chronic liver disease (cACLD) patients[32]. In another recent meta-analysis of chronic viral hepatitis patients, LS cut-offs < 13.6 kPa ruled out CSPH [pooled sensitivity: 96%; 95% confidence interval (CI): 93%-97%] and > 22 kPa ruled in CSPH (pooled specificity: 94%; 95%CI: 86%-97%), confirming the Baveno VI agreement.

In a cohort study involving 343 persons diagnosed with chronic liver disease, of whom 60 were diagnosed with liver cirrhosis, it was shown that for each incremental unit in the natural logarithm of LS, there was a 14.7-fold increase in the probability of liver-related events ($P < 0.001$). When the LS value is more than 30 kPa, liver cirrhosis is usually clinically evident, with the ubiquitous presence of ascites and serum markers better predicting mortality within 12 mo. However, in another large meta-analysis with 35249 participants, LS displayed a nonlinear relationship with the risk of liver-related events. These findings suggest a modest increase in the risk of liver-related events and death associated with increased LS. However, further research is needed to develop models that can accurately predict personalized risk stratification based on LS and other variables such as albumin, bilirubin, and prothrombin time.

Differentiation of cirrhotic aetiologies: Disease aetiology significantly affects the liver's response to inflammation. Hepatitis C virus (HCV) patients with identical elevated transaminases and fibrosis stages showed lower LS values than

lobular alcohol liver disease (ALD) patients. Hence, inflammatory localization (portal *vs* lobular) may also determine LS. Also, the liver size to LS ratio between HCV and ALD is significantly different. The liver size in patients with HCV constantly decreases as fibrosis advances, whereas in patients with ALD, it first increases until reaching an LS of 30 kPa, after which it begins to decline. Simultaneous liver-spleen elastography can help distinguish cirrhosis from intrahepatic non-cirrhotic PH. Prehepatic pathologies, such as portal vein thrombosis, are associated with elevated spleen stiffness (SS)/LS ratios. A post-hepatic pathology, such as liver congestion in HF, will result in an SS/LS ratio as low as 0.3. Consequently, the finding of a disproportionate increase in SS *vs* LS in a patient with PH symptoms and the finding of an LS 20 > kPa in a patient suspected of cirrhosis due to PH should prompt further investigations to rule out porto-sinusoidal vascular disease and other causes of non-cirrhotic intrahepatic PH[33]. SS/LS ratios may provide additional non-invasive and valuable information for the differential diagnosis of liver disease.

Moreover, SS can be employed to distinguish between acute and chronic liver injury, as SS values are notably elevated in individuals with chronic liver damage compared to those with acute liver damage, even though LS levels are similar. In terms of predicting esophageal variceal bleeding (EVB), SS exhibited a superior AUROC value than spleen diameter, platelet count, and LS (0.857, 0.746, 0.720, and 0.688, respectively)[34]. Similar SS cut-off values for EVB were found in a recent research by Wang *et al*[35], with SS being superior to LS in predicting EVB (SS = 45.5 kPa and AUROC = 0.923 *vs* LS = 29.6 kPa and AUROC = 0.860). Additional long-term research is necessary to further evaluate the effectiveness of these elastography parameters and their efficacy.

Prediction of complications: Complications may frequently occur in patients with liver cirrhosis, necessitating ICU admission. These complications are associated with increased morbidity and mortality. Hence, identifying patients at risk and early detecting these complications may aid in instituting therapeutic measures and improving clinical outcomes. A meta-analysis evaluating the diagnostic accuracy of TE for PH reported a high accuracy for diagnosing PH and esophageal varices with an AUROC of 0.93 and 0.84, respectively[36]. High LSM, as evaluated by TE, has also been shown to correlate with the development of hepatocellular carcinoma, the most dreaded complication and the commonest cause of death among CLD patients[37,38].

Response to treatment: It is still unknown how, in the future, individual patient profiles of cirrhotic patients by LSM and SS measurement (SSM) may contribute to optimizing therapeutic management [for example, by transjugular intrahepatic portosystemic shunt (TIPS) or portal pressure lowering medications]. Kim *et al*[39] explored SS for this purpose because LS cannot be utilized to monitor PH under a non-selective beta blocker (NSBB). Before and after titrating NSBB (carvedilol), they assessed SS in 106 individuals with cirrhosis and high-risk oesophageal varices. By evaluating the HVPG at the same time points, they could also assess the hemodynamic response to NSBB. The hemodynamic response could be accurately predicted using the computed prediction model (model = 0.0490-2.8345 SSM) and 0.530 as the cut-off value (AUROC = 0.803). The model retained a strong capacity for discrimination in the validation cohort (AUROC = 0.848)[39].

Studies on LSM after TIPS insertion revealed an overall decline, but no significant correlation was detected between the decline in LS and that in portal pressure[40]. More recently, it has been proposed that only some patients' LS would drop after TIPS; patients with an early LS decline would demonstrate a positive outcome after TIPS, whereas patients with an early LS increase after TIPS would have a negative prognosis[41]. LS increase after TIPS could be due to an inflammatory response, triggering acute on chronic liver failure and death in this population.

Post liver transplant

Prognostication: The standard of care for patients with end-stage liver disease and those with inoperable liver malignancies is LT. Hepatic fibrosis is an important predictor of clinical outcomes in LT recipients. Advanced hepatic fibrosis is a surrogate for graft cirrhosis and hepatic decompensation and has been linked to both liver-related and non-liver-related outcomes. LSM can perform a role in the context of liver graft transplantation. In their study, Nacif *et al*[42] employed the technique of time-to-event analysis to assess and evaluate the mortality risk among individuals with end-stage cirrhosis who were on the liver transplant waiting list with and without the presence of hepatocellular carcinoma. Like the well-known model for end-stage liver disease (MELD) score, increased LS was associated with more significant mortality. The mean MELD score was 14.7 ± 6.4, whereas the mean LS was 32.7 ± 22.5 kPa. The survived group had a mean LS of 31.6 ± 22.2 kPa, in contrast to a mean LS of 50.8 ± 9.9 kPa seen in the non-surviving group (P = 0.098). Additionally, the surviving group showed higher MELD scores than the non-surviving group (P = 0.035). Therefore, elastography has the potential to serve as a valuable non-invasive tool in the diagnosis of cirrhosis and hepatocellular carcinoma, as well as in predicting mortality. However, further prospective data is required to support these findings.

Acute transplant rejection: Acute allograft rejection is still a significant postoperative complication following LT, affecting approximately 30% of recipients. It is an inflammatory process involving endothelial and biliary epithelial cells, typically within the first week after transplantation. Late episodes, *i.e.*, those that occur after the first year, suggest insufficient immunosuppressive therapy. Acute rejection is generally diagnosed using clinical, laboratory, and histopathologic criteria. Additionally, the inflammatory process that characterizes allograft rejection may exacerbate LS. In the study conducted by Nacif *et al*[42], graft damage was determined when the LS exceeded 7.9 kPa, but graft damage was ruled out when LS was below 5.3 kPa (AUROC = 0.93; P = 0.001). A distinct study found that LS cut-off values of more than 8.5 kPa accurately predicted the occurrence of moderate to severe acute rejection with a specificity of 100% and an AUROC value of 0.924. Conversely, LS values below 4.2 kPa effectively ruled out the presence of any acute rejection[43]. Identical outcomes were also observed in the AMUSE trial[44].

LIMITATIONS

Like any other clinical test, FibroScan has its own set of limitations. Even though TE is reported to be an operator-independent procedure with low inter-observer variability[45], poor operator technique may increase variability in the results[46]. Hence, at least ten measurements are required to ensure the reliability of the results. Patient positioning is also crucial for capturing correct readings[47]. Ideally, it is performed using an intercostal approach with the patient lying supine with the right arm in maximum abduction[47].

Several physiological or patient factors may also affect the accuracy of TE. Fatty meals[48], water intake[49], excessive exercise, and morbid obesity (BMI > 30 kg/m^2) may all affect its accuracy, and hence, it is recommended that FibroScan be performed in a fasting patient[5,45,50]. Even alcohol consumption may also affect LSM measurement using FibroScan; therefore it is recommended to repeat TE after a week of abstinence[51]. Apart from liver fibrosis, LS may be altered in several other clinical conditions, including cholestasis, congestion, hepatitis, liver necrosis, malignancy, and liver storage disorders, which may lead to false positive results[46,50-52].

Different cut-offs for LSM are recommended for the diagnosis of different liver diseases. On the one hand, cut-offs of < 7 kPa and > 12 kPa are recommended to rule out and rule in hepatitis B and hepatitis C related cACLD, whereas cut-offs of < 7 kPa and > 12 kPa are recommended to rule out and rule in alcohol and non-alcoholic fatty liver disease related cACLD[7,53]. Additionally, these cut-offs are still evolving as more literature becomes available.

Most of the data regarding TE has originated from studies conducted in relatively stable patients with chronic liver disease, and there is a dearth of data regarding its efficacy among critically ill patients. Several factors may affect the accuracy of TE, especially in critically ill patients and it is estimated that LSM cannot be accurately measured in about 30% of ICU patients[12]. Moreover, its efficacy may be further affected during the ICU course because of volume overload and the need for mechanical ventilation. FibroScan testing may be compromised in critically ill patients because of ascites, difficult positioning, feeding, invasive mechanical ventilation, and hemodialysis[7,12,47,48,54]. Even phases of respiration in which readings have been obtained may affect the reliability of LSM[55].

For SS, in addition to the technical restriction indicated for LS assessment, the operator cannot locate the splenic parenchyma in some individuals due to the spleen surface being smaller than the liver. However, with operator expertise, it has decreased over time. Another technical consideration for SS measurement by TE is that SS is performed using a probe approved solely to measure LS. Indeed, the FibroScan acquisition parameters were tuned for stiffness assessment for liver tissues, particularly in low-frequency excitation. Thus, utilizing the FibroScan on the spleen may overestimate stiffness values[56].

CONCLUSION

Detection of liver fibrosis is an important component of liver function evaluation as it correlates with severity and prognosis across different aetiologies causing liver dysfunction. Even though liver biopsy remains the gold standard for assessing the extent and severity of liver fibrosis, it has several limitations, including its invasive nature, high cost, need for clinical expertise, and relatively high complication rates. These complications may be more severe in critically ill patients, necessitating the preferable use of non-invasive and easily repeatable tests like TE for evaluating liver fibrosis. These tests may help in staging and monitoring fibrosis and its related complications and provide a reasonable alternative to more invasive testing. Evolving literature suggests several clinical applications; however, its application has limitations, which must be considered while performing TE, especially in ICU patients.

FOOTNOTES

Author contributions: Kataria S and Juneja D researched the subject, performed data accusation, and performed the majority of the writing; Singh O provided inputs in paper writing and reviewed the final draft.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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S-Editor: Wang JJ
L-Editor: Wang TQ
P-Editor: Yu HG

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