Role of Transient Elastography (Fibroscan) in Differentiating Severe Acute Hepatitis and Acute on Chronic Liver Failure

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Introduction: It is difficult to differentiate acute severe hepatitis (AH) with acute on chronic liver failure (ACLF). Aim was to study the role of transient elastography (Fibroscan) in identifying the patients with AH and ACLF. **Materials and methods:** Consecutive patients of severe AH or ACLF presented within two weeks of jaundice were enrolled. LSM and liver function tests were done at admission, week 1, 4 and at 6 months. Diagnosis of ACLF was based on documenting cirrhotic morphology on imaging and/or liver biopsy and follow-up of these patients for six months. Similarly, AH patients were diagnosed based on serology, no features of cirrhosis on imaging and follow-up of these patients for 6 months documenting reversal of liver stiffness measurement (LSM) to normal. **Results:** 104 patients were included in the final analysis (AH, $n = 59$, ACLF, $n = 45$). Out of 59 patients in severe AH group, etiology of acute hepatitis included hepatitis A (HAV, $n = 22$), hepatitis E (HEV, $n = 21$), hepatitis B (HBV, $n = 4$), indeterminate ($n = 8$) and drug induced liver injury ($n = 4$). Similarly for ACLF, the causes of chronic liver disease were alcohol ($n = 26$), hepatitis B ($n = 7$), hepatitis C ($n = 2$) and cryptogenic ($n = 10$). Patients with ACLF were significantly older, had low hemoglobin, low albumin, high bilirubin and lower transaminases level compared to severe AH at admission. LSM was higher in patients with ACLF compared to severe AH (61 ± 18 kPa vs 15 ± 6.4 kPa, $P = 0.001$) at admission. On multivariate analysis of noninvasive tests only LSM was found to differentiate AH with ACLF significantly. When we took a cutoff of 26 kPa the sensitivity and specificity of diagnosis of ACLF were 96% and 93%, respectively, with area under the curve was 0.98 (0.95–1.005), $P = 0.001$. **Conclusion:** LSM could differentiate patients with severe AH and ACLF at admission. (J CLIN EXP HEPATOL 2015;5:303–309)

INTRODUCTION

Transient elastography (Fibroscan; Echosens, Paris, France) is a rapid, non-invasive, and reproducible method of measuring liver stiffness. Liver stiffness measurement (LSM) has been shown to be a reasonable tool to quantify liver fibrosis in chronic liver diseases due to varied etiology.¹ The diagnostic accuracy of transient elastography (TE) for liver fibrosis is supported by a recently published meta-analysis.² However, several studies have indicated that the LSM value can be significantly influenced by major changes in aminotransferases level in patients with chronic viral hepatitis and that LSM is unreliable for diagnosing underlying liver fibrosis in

patients with acute liver damage.^{3,4} The current “gold” standard for assessment of liver fibrosis remains the liver biopsy. However, liver biopsy is an invasive procedure associated with both patient morbidity, and less commonly, mortality. It is also contraindicated to do percutaneous biopsy in patients with deranged coagulation profile as in patients with severe acute hepatitis and acute on chronic liver failure (ACLF).

ACLF is a syndrome characterized by acute deterioration in liver function tests in a patient with underlying known or unknown chronic liver disease.⁵ Identifying patients of ACLF early is of great importance as it would allow these patients, at high risk of end-organ failure-related death, to receive specific treatment, intensive management and early listing for transplantation and referral to tertiary care center. It is important to differentiate acute hepatitis due to hepatitis B (AVH-B) and chronic hepatitis B with severe reactivation as they have different prognosis and may require differing therapeutic strategies. The majority of patients with AVH-B will resolve spontaneously, and treatment may be required only in a few patients with severe/fulminant disease. On the other hand, patients with severe reactivation usually require therapy, as the hepatocellular dysfunction may lead to hepatic decompensation. However often it is difficult to differentiate acute

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Abbreviations: ACLF: acute on chronic liver failure; AH: acute severe hepatitis; AST/ALT: aspartate transaminase and alanine transaminases; LSM: liver stiffness measurement; SOFA: sequential organ failure assessment score; TE: transient elastography

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severe hepatitis (AH) with ACLF at the time of admission, as patient did not give any history of underlying chronic liver disease. It is only after a panel of investigations that are expensive and time taking that one makes a diagnosis of ACLF. We hypothesize that patients with severe acute hepatitis will have significantly lower LSM than patients of ACLF, as there is no fibrosis in patients with severe AH and could be of help to differentiate between these two at admission.

MATERIALS AND METHODS

From May 2013 to January 2014, we prospectively enrolled consecutive patients suspected to have either severe AH or ACLF and who were admitted to our Hospital. Diagnosis of ACLF was based on documenting cirrhotic morphology on imaging and/or liver biopsy and follow-up of these patients for six months. Similarly AH were diagnosed based on serology, no features of cirrhosis on imaging and follow-up of these patients for 6 months documenting reversal of LSM to normal. Severe AH was defined as an elevation of serum alanine aminotransferase (ALT) to more than five times the upper limit of normal in a previously healthy person and serum bilirubin of more than 5 mg/dl and international normalized ratio (INR) more than 1.5. We took this definition to define severe AH as bilirubin more than 5 and INR more than 1.5 often creates confusion at admission to rule out any underlying chronic liver disease in such patients. ACLF was defined as acute hepatic insult manifesting as jaundice (≥ 5 mg) and coagulopathy (INR ≥ 1.5), complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease.⁵

Exclusion criteria were as follows: obstructive hepatobiliary pathology, hepatobiliary malignancy, severe cardiac problems, gross ascites, hepatic encephalopathy at the time of admission and not willing for follow-up. This study was approved by the Institutional Review Board of Hospital and written informed consent was obtained from each patient. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. The aim of this study was to compare the LSM values in patients of ACLF and severe AH at the time of admission and follow-up and its role in differentiating the two at admission.

Etiology work up for AH and ACLF

For the determination of the etiology of acute hepatitis, a detailed physical examination and history taking was performed in all patients, including past history of exposure to hepatotoxic drugs and alcohol intake. Acute hepatitis A and E was defined by positive immunoglobulin (Ig) M anti-hepatitis A virus (HAV) or positive immunoglobulin (Ig) M

anti-hepatitis E virus (HEV) in serum. Acute hepatitis B was defined by positive HBsAg, positive IgM antibody to hepatitis B virus core antigen (anti-HBc). The HBV DNA level was also measured and liver biopsy was done in case of suspected underlying chronic liver disease. If patients had features of underlying chronic liver disease on imaging like coarse echotexture of liver, portal vein >14 mm, splenomegaly or presence of esophageal varices, a diagnosis of chronic hepatitis B with severe reactivation was made. If these features were not present, then absence of IgM Hbc and HBV DNA $>10^5$ copies/ml was taken as chronic hepatitis B with reactivation along with liver biopsy if available.⁶ The diagnosis of drug-induced hepatitis was made according to the criteria of an international consensus meeting.⁷ Liver biopsy (either percutaneous or transjugular) was performed when the etiology of acute hepatitis was not clearly identified by history taking and serological examination.

Diagnosis of ACLF was made after taking detailed history and investigation to document the evidence of cirrhosis and acute event leading to decompensation. Cirrhosis was diagnosed based on radiological (ultrasound and computed tomography), clinical, and biochemical parameters and liver biopsy whenever needed. Upper Gastrointestinal endoscopy was also done in all patients. Liver biopsy was done if needed and liver fibrosis and necroinflammatory activity were evaluated semi-quantitatively according to the METAVIR scoring system as follows: F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis and few septa; F3, numerous septa without cirrhosis; and F4, cirrhosis. METAVIR activity score was defined as: A0, none; A1, mild; A2, moderate; and A3, severe.⁸ Acute event was diagnosed by taking a detailed history of alcohol intake, drug history, bleed and getting all viral markers, blood culture and ascitic culture done. All patients who remained admitted in hospital underwent complete liver function tests and INR on every third day or whenever considered necessary depending upon patient condition. Sequential organ failure assessment score (SOFA) was also calculated at the time of admission in all patients. Ultrasound abdomen or computed scan of the abdomen was also repeated during hospital stay if needed. Once the patient got discharged the patient was instructed to come weekly for follow-up for the initial four weeks and then on monthly basis or earlier if required for six months.

Liver stiffness measurement

LSM was performed using the Fibroscan (Echosens, Paris, France). This procedure has been well described previously.⁹ Only patients with at least ten valid measurements and a success rate of over 60% were included. Liver stiffness scores were expressed in units of kilopascals (kPa). This was performed in all patients at the time of

admission, week 1 and 4, and after 6 months from the time of admission in all patients.

Treatment and follow-up of patients

All enrolled patients were admitted in view of clinical symptoms and rising INR. No patients in severe AH received any antiviral treatment for hepatitis B and E. All patients with severe AH received multivitamin and no diet restriction. Supportive therapy with intravenous fluids was given if patient is not able to take orally and multivitamins were given to all patients. Patients with ACLF due to hepatitis B flare was given tenofovir and patients with alcoholic hepatitis and alcoholic liver disease patients were given pentoxifylline and other supportive treatment. Steroids were not given in any patients, as patients were not found to be fit for this therapy. All patients had repeat LSM at week 1 and 4 and week 24.

Statistical analysis

Patient characteristics are given as means standard deviation. The paired Student's *t*-test was applied for comparison of laboratory findings in the same subject. Sensitivity and specificity of LSM to differentiate severe AH and ACLF was calculated using receiver-operating characteristic curves. The Pearson correlation analysis was used to identify the correlations between the LSM value and other variables at diagnosis. The linear regression analysis with variables showing significance was used to investigate the contribution of each variable toward differentiating ACLF and severe AH. Multiple linear regression analyses were performed to identify independent variables associated with differentiation between severe AH and ACLF and mortality in patients. A two-tailed *P*-value <0.05 was considered significant. All statistical analyses were performed with SPSS 12.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 116 patients were recruited during the study period. Ten patients were excluded due to inadequate follow-up, and further two patients were excluded due to success rate of 60% in any one of their LSM at the four different time points. One hundred and four patients were included in the final analysis. The patient's demographic, baseline laboratory data, and LSM were summarized in Table 1. All patients were recruited within two weeks of onset of jaundice.

Of 59 patients enrolled in severe AH group, etiology of acute hepatitis were hepatitis A (HAV, *n* = 22), hepatitis E (HEV, *n* = 21), hepatitis B (HBV, *n* = 4), indeterminate (*n* = 8) and drug induced liver injury (*n* = 4). None of the patients in AH had features of overt hepatic encephalopathy at admission or during follow-up. None of these patients were evaluated for minimal hepatic encephalopathy. Similarly for ACLF the causes of chronic liver disease were alcohol (*n* = 26), hepatitis B (*n* = 7), hepatitis C (*n* = 2) and cryptogenic (*n* = 10). The acute event in patients with ACLF was acute viral hepatitis (*n* = 27), which includes (HAV, *n* = 6), (HEV, *n* = 14), and (HBV, *n* = 7). Alcoholic hepatitis (*n* = 16), drug induced injury (*n* = 1), and unknown (*n* = 1) were the acute events in rest of the patients. No patient in severe AH showed a coarse echo pattern or irregularities of the liver surface in ultrasound abdomen. While ultrasound showed coarse liver echotexture, dilated portal vein (>14 mm) in patients with ACLF (*n* = 39) which were correlated with computed scan of abdomen. Transjugular liver biopsy was done in 6 patients in ACLF group during hospital stay (4 in cryptogenic and 2 in HBV related liver disease), which revealed cirrhosis (F4). Eight patients (17.5%) initially classified under ACLF group due to presence of coagulopathy and mild ascites (4 indeterminate group, 2 HBV and 2 DILI group) were

Table 1 Baseline Characteristic of Enrolled Patients.

Parameters	ACLF (<i>n</i> = 45)	AH (<i>n</i> = 59)	<i>P</i>
Age (year)	45 ± 11	37 ± 16	0.005
Gender (F:M)	4:41	18:41	0.008
Hb (g/dl)	10.4 ± 2.0	11.9 ± 3.8	0.001
TLC (10 ³ /ml)	10.2 ± 6.6	10.1 ± 5.6	0.89
Platelet count (10 ³ /ml)	140 ± 86	228 ± 90	0.001
Total bilirubin (mg/dl)	17.8 ± 7.8	12.8 ± 7.9	0.001
AST (IU/L)	159 ± 87	972 ± 1155	0.001
ALT (IU/L)	165 ± 69	705 ± 852	0.001
INR	1.9 ± 0.5	1.8 ± 0.6	0.34
Varices (small:large)	21:3	0	–
SOFA score	10.1 ± 2.1	5.7 ± 0.7	0.00

Hb, hemoglobin; AST/ALT, aspartate transaminase and alanine transaminases; INR, international normalized ratio; TLC, total leukocyte count; SOFA, sequential organ failure assessment.

Table 2 Baseline and Follow-up Data of Patients with ACLF and AH.

Parameters	ACLF (n = 45)				AH (n = 59)			
	B (n = 45)	Week 1 (n = 45)	Week 4 (n = 38)	Week 24 (n = 29)	B (n = 59)	Week 1 (n = 59)	Week 4 (n = 59)	Week 24 (n = 59)
Bilirubin (mg%)	17.8 ± 8	18 ± 9	14 ± 8	2.2 ± 0.8	13 ± 8	10.2 ± 7	4.4 ± 3.5	1.0 ± 0.2
AST (IU/L)	165 ± 69	118 ± 75	60 ± 28	87 ± 41	705 ± 852	363 ± 580	50 ± 16	34 ± 18
ALT (IU/L)	159 ± 87	69 ± 66	53 ± 25	57 ± 20	972 ± 1155	488 ± 698	51 ± 16	49 ± 19
ALB (g%)	2.4 ± 0.5	2.6 ± 0.4	2.6 ± 0.4	2.4 ± 0.3	3.1 ± 0.6	3.2 ± 0.6	3.2 ± 0.7	3.8 ± 0.4
Fibroscan (kPa)	61 ± 18	59 ± 18	57 ± 19	41 ± 17	15 ± 6.4	11.3 ± 4.7	6.2 ± 2.2	5.8 ± 1.2

AST/ALT, aspartate transaminase and alanine transaminases; ALB, albumin.

later diagnosed as AH during follow-up by doing liver biopsy and reversal of LSM to <6 kPa. Their baseline LSM was 27.4 ± 3.2 kPa. These patients were relabeled as AH and included in AH group at baseline. Biopsy in these patients did not reveal any fibrosis. None of the patients who were initially labeled as AH were classified as ACLF during follow-up. Biopsy was done in 4 patients during hospital stay in AH group (2 HBV and 2 indeterminate group) and it did not show any features of fibrosis.

Upper gastrointestinal endoscopy was done in all patients. Esophageal varices were present in 24 patients with ACLF, while none with severe AH had varices. Patients were followed up with serial liver function tests, INR, and LSM measurement as shown in Table 2.

LSM at admission in differentiating severe AH and ACLF and in predicting 6-month mortality

Patients with ACLF were significantly older and amongst noninvasive tests patients with ACLF had low hemoglobin, low albumin, high bilirubin and significantly lower AST and ALT level compared to patients with severe AH at admission (Table 1). LSM was also significantly lowered in patients with severe AH compared to patients with ACLF. During follow-up patients with ACLF and severe AH who showed improvement in total bilirubin and AST/ALT had fall in LSM values (Table 2). On multivariate analysis of noninvasive tests only LSM had shown significant difference in differentiating between severe AH and ACLF (Table 3). Presence of esophageal varices which is invasive test confirms presence of chronic liver disease and portal hypertension hence diagnosis of ACLF was confirmed so this was not kept in multivariate analysis.

LSM was done at the time of admission in all patients. LSM was significantly higher in patients with ACLF compared to patients with severe AH (61 ± 18 kPa vs 15 ± 6.4 kPa, $P = 0.001$) at admission. When we took a cutoff of 26 kPa the sensitivity and specificity of diagnosis of ACLF was 96% and 93% respectively with area under the curve was 0.98 (0.95–1.005), $P = 0.001$ (Figure 1). Follow-up parameters of two groups (ACLF and AH) were shown in Table 2 and Figure 2.

Sixteen patients (36%) died between week 3 and week 24 and all these patients were from ACLF group. Ten patients had alcoholic liver disease; five had cryptogenic liver disease and one had hepatitis B related underlying chronic liver disease. Alcoholic hepatitis was the precipitating agent in 10, acute hepatitis A in 3 and acute hepatitis E in three patients. Post mortem liver biopsy was done in 9 patients with underlying alcoholic liver disease and all had shown cirrhosis.

LSM value 55.6 kPa had sensitivity and specificity of 94% and 81% respectively with AOC (0.91, 0.85–0.96, $P = 0.001$) in predicting mortality within 6 months of hospital admission in patients with ACLF (Figures 3 and 4). SOFA score was significantly high in patients who died versus who did not in ACLF group (11.4 ± 2.3 vs 9.3 ± 1.4 , $P = 0.001$). On multivariate analysis only SOFA was the predictor of mortality Exp(B) 1.89 (95% CI 1.89–3.07, $P = 0.001$).

DISCUSSION

In this study we found that LSM done at the time of admission could differentiate patients with severe AH

Table 3 Multivariate Analysis Showing Difference in Severe AH and ACLF for Diagnosis.

Parameters	B	S.E.	Exp(B)	P
Age	0.000	0.061	0.999	0.99
Total bilirubin	−0.02	0.08	0.98	0.81
AST	0.009	0.008	1.009	0.25
ALT	0.001	0.003	1.001	0.86
Albumin	−0.82	1.58	0.439	0.60
INR	−1.64	1.62	0.193	0.31
Platelet	0.008	0.01	1.008	0.39
LSM	−0.303	0.130	0.738	0.02

AST/ALT, aspartate transaminase and alanine transaminases; INR, international normalized ratio; INR, international normalized ratio; LSM, liver stiffness measurement.

Figure 1 Receiver operative curve of LSM for the diagnosis of severe AH and ACLF.

Figure 2 Box plot diagram showing LSM at different intervals in patients with ACLF and severe AH.

Figure 3 Receiver operative curve for LSM in predicting mortality at 6 month in patients with ACLF.

Figure 4 Kaplan Meier plot for survival in patients with ACLF with LSM >55.6 kPa.

and ACLF. LSM value of 26 kPa and higher could differentiate severe AH and ACLF with sensitivity and specificity of 96% and 93% respectively for diagnosing ACLF.

There is no universally accepted definition of ACLF; however, it is recognized as an entity characterized by decompensation from an underlying chronic liver disease associated with organ failure that conveys high short-term mortality, with alcoholism and infection being the most frequent precipitating events.^{10,11} It is important for the clinician to differentiate acute liver failure clearly from both acute-on-chronic and acute-on-cirrhosis liver failure, both of which have a much poorer prognosis. However there is no uniform definition of ACLF.¹² In a German study by Canbay et al.¹² ACLF defined when there is chronic liver disease like HBV, NAFLD etc. while acute on cirrhosis liver failure was defined when there were features of cirrhosis.¹² Patients with ACLF have a short-term mortality of 50–90%, and when compared with that observed in cirrhotic patients without ACLF, even with the same MELD scoring, mortality is higher in ACLF.^{13,14} Various scoring systems have been devised for prognosticating patients with ACLF with various sensitivity and specificity.^{10,15} Differentiating ACLF and severe AH is difficult at admission in some patients who never been symptomatic earlier. Diagnosis of ACLF is important as early management of precipitating factor in ACLF patient decreases mortality for example in acute reactivation of chronic hepatitis B need immediate antiviral treatment compared to acute hepatitis due to hepatitis B. In our study there was no mortality in severe AH group however 16 (36%) patients died in follow-up in ACLF group. LSM has never been evaluated in patients with ACLF to predict mortality in

such subgroup. We found in this study that LSM value 55.6 kPa or higher had sensitivity and specificity of 94% and 81% respectively in predicting mortality within 6 months of hospital admission in patients with ACLF. However SOFA score was the only parameter on multivariate analysis to predict mortality. Hence future studies to evaluate the role of LSM in predicting mortality and its incorporation in others predictive models needs further evaluation.

TE is a novel and promising technique for the rapid and noninvasive assessment of fibrosis progression in viral and nonviral chronic liver disease patients. This technique has been subjected to extensive validation in cross-sectional and longitudinal studies all over the world.¹⁶ A major endeavor in this process of validation concerns the identification of potential factors leading to an overestimation or underestimation of the fibrotic transformation of liver tissue assessed by this technique. In this context, extensive inflammatory infiltration, hepatocyte swelling, and tissue edema, which are relevant components of the chronic wound healing and fibrogenic process, could represent important confounding factors.^{17,18} Arena et al.⁴ had shown that in patients with AVH, LSM does not represent a reliable instrument to detect the presence of advanced fibrosis and cirrhosis in patients presenting with a clinical picture of acute hepatitis. It was found that the mean LSM in patients with AVH was 12.7 ± 5.7 kPa and their mean ALT (2004.9 ± 1115.4 IU/L) and bilirubin was 5.9 ± 5.6 mg/dl. We found in our study that in patients with severe AH the mean LSM was 15 ± 6.4 kPa which on follow-up at 6 months had decreased significantly to less than 7 kPa in all patients with severe AH. This reconfirms that in case of acute hepatitis LSM is not a reliable tool to assess fibrosis. However we also found that taking a cut off of 26 kPa LSM could differentiate severe AH and ACLF with sensitivity and specificity of diagnosing ACLF was 96% and 93% respectively. Hence LSM measurement still holds its value in discriminating severe AH and ACLF at the time of admission. We did not do biopsy in patients with severe acute hepatitis as radiological parameter suggest no features of underlying chronic liver disease in these patients which was reconfirmed on repeat ultrasound in these if needed. However in two patients initially labeled as severe AH, liver biopsy was done to know the etiology (indeterminate group) as other viral and metabolic factors were negative and in two patients with hepatitis B to know any fibrosis and in these patients' biopsy revealed no fibrosis. Similarly liver biopsy was not done in patients of ACLF as patients were initially sick. In patients of ACLF in whom radiological, biochemical, and endoscopic findings were suggestive of underlying chronic liver disease biopsy was not done. TJLB was done in 6 patients in ACLF group during hospitalization and all patients revealed F4 fibrosis (four patients with cryptogenic liver disease and two patients with hepatitis B related cirrhosis). Postmortem liver biopsy was done in 9 patients with ACLF and

revealed cirrhosis in all. Eight patients who were initially classified as ACLF due to coagulopathy with ascites, had liver biopsy on follow-up after resolution of ascites and coagulopathy and it did not reveal any features of fibrosis and hence were reclassified as AH.

Recent results have revealed a correlation between liver injury and organ stiffness as measured by TE, and this suggests that this technology indirectly monitors early fibrosis as well as edema and inflammation. In these cases, fibrosis had been excluded by biopsy. However, fibrosis is in homogeneously distributed in the liver suggests that locally confined biopsy cannot reliably determine fibrosis.¹⁹ In a study by Dechêne et al.²⁰ twenty-nine patients with acute liver failure consistently revealed significant increases in serum tissue inhibitor of metalloproteinases 1 and serum levels of matrix metalloproteinase 1 levels as well as histological evidence for collagen formation and α -SMA expression. These findings clearly demonstrate ongoing profibrotic processes together with increased hepatic stellate cells activity (HSC). Positive correlations between LSM, the degree of liver cell damage, and the intensity of HSC activation suggest that fibrosis is a response to ALF in an attempt to repair damaged tissue. However in our study severe AH patients did not had features of ALF as overt encephalopathy was not present. We did not find any sign of fibrosis in patients with severe AH however markers like serum tissue inhibitor of metalloproteinases 1 and serum levels of matrix metalloproteinase 1 were not measured in this study.

Strength of this study was that it included patients with severe acute hepatitis and ACLF and was followed with serial LSM measurement till 6 months. This is the first study which showed that one can differentiate early between severe AH and ACLF by doing LSM measurement in early stage of disease progression. Drawback of this study was that liver biopsy was not done in all patients with severe AH. However all radiological and biochemical parameters were done and none showed any evidence of underlying chronic liver disease. Patients were followed up with LSM and liver function tests and it showed significant improvement and LSM normalizes to that of healthy control in our population as done in previous study.¹⁸ To conclude LSM is useful in patients with severe AH and ACLF at the time of admission and taking a cutoff of 26 kPa one could differentiate between the two with high sensitivity and specificity.

CONFLICTS OF INTEREST

The authors have none to declare.

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