



SCIREA Journal of Clinical Medicine

ISSN: 2706-8870

<http://www.scirea.org/journal/CM>

May 7, 2024

Volume 9, Issue 2, April 2024

<https://doi.org/10.54647/cm321260>

## **Imaging Inflammation in Compensated Advanced Chronic liver disease as a new predictor for liver decompensation.**

**Atul Kapoor<sup>1,\*</sup> Aprajita kapur<sup>1</sup>**

<sup>1</sup> Department of Radiology, Advanced Diagnostics and institute of Imaging. Amritsar. Punjab, India.

\* Correspondance: Dr Atul Kapoor Email: [masatulak @aim.com](mailto:masatulak@aim.com)

### **ABSTRACT:**

#### **Introduction:**

Alcohol and Non-alcoholic fatty liver disease (NAFLD) are the commonest causes of advanced chronic liver disease (ACL D) worldwide. Various imaging are commonly used in the diagnosis and follow up of these patients. Child Pugh and Model of end stage liver disease systems are used for survival and three mortality of decompensated ACL D patients. However there is a need for imaging biomarkers for compensated ACL D (cACL D) patients to predict likelihood of decompensation. With increasing stress on the role of systemic inflammation as a causative agent in the progression and decompensation of ACL D patients the new imaging technique of shear wave elastography with dispersion of liver (SWD) and small bowel (SBD) were evaluated alongwith liver stiffness estimation.

**Material and Methods:** 61 patients with cACL D with NAFLD or history of alcohol ingestion were enrolled after informed consent and were followed for a period of three months for any decompensation i.e. ascites, gastrointestinal bleed or encephalopathy. All

patients underwent a fasting ultrasound examination with shear wave elastography and liver stiffness alongwith shear wave dispersion (SWD) and small bowel inflammation (SBD). Follow up examinations were done at 30, 45 and 90 days or any time in between if there was any clinical evidence of decompensation. The patients were divided into four groups I-IV based on SWD and SBD findings as group I(A0B1),group II(A1B0), group , Group III(A1B1), group (A0B0). Statistical analysis was done to assess the significance of differences in the groups and incidence of decompensation recorded in each group. A prediction model was developed using machine learning based on above parameters to predict decompensation in a 90 day period.

**Results:** Group II and III performed the largest groups with 44 patients. Statistically significant differences were seen in SWD and SBD in all the groups ( $p < 0.001$ ). A good linear regression of 0.52 and 0.64 was seen between SWD and SBD and liver stiffness. The study showed decompensation in 12/61 patients the largest were number being in the groups III and II with decompensation likelihood of 27% and 24% respectively using Kaplan Meyer survival plot.SBD showing a highest hazard ratio of 1:24.4 while SWD alone had hazard ratio of 1:2.4.

**Conclusion:** The use of SWE markers is a novel way to evaluate patients with cACLD patients and using machine learning model predict 3 month likelihood of decompensation with 75% accuracy.

**KEYWORDS:** Compensated advanced chronic liver disease, Cirrhosis, shear wave elastography, Shear wave dispersion, decompensated advanced liver disease.

## INTRODUCTION

Liver cirrhosis is an end stage hepatic disease characterized by a progressive replacement of the functional hepatic architecture by non-functional fibrotic tissue. The two commonest causes of cirrhosis are alcohol induced liver injury (AD) and non-alcoholic fatty liver disease (NAFLD) (1). There is a sustained inflammatory reaction in the liver due to the direct effects of the above two diseases leading to release of inflammatory pro cytokines which lead to tissue regeneration and fibrosis (2). The initial stage of disease, which is compensated for advanced chronic liver disease, is asymptomatic and remains undetected. This is followed by a second stage of decompensation i.e. ascites, variceal bleeding or encephalopathy and even

acute chronic liver failure (3). The driving factors between the two stages are the presence or absence of organ inflammation. There is formation of degradation associated molecular patterns (DAMP) in the liver in alcohol liver disease and pathogen associated molecular patterns(PAMP) due to constant bacterial translocation of altered gut microbiota leading to continuous systemic and liver inflammation, thus causing deteriorating liver function, thus leading to decompensation (4). Coupled with this is liver cirrhosis induced immune dysfunction of macrophages and other cells of innate immunity which causes further deterioration. Blood tests like C reactive proteins and inflammatory pro markers like IL-6 have been proposed to assess for presence of ongoing inflammatory activity in such patients (5).

Due to advances in the non-invasive imaging techniques like liver elastography for liver stiffness estimation and shear wave dispersion appear as attractive tools in determining not only the extent of liver fibrosis but can be used to quantify liver and bowel wall inflammation(6 -7). Contrary to the traditional view that AD occurs due to certain precipitants, CANONIC study revealed that it was due to systemic inflammation (8). So far there has been no study designed to use imaging parameters to predict near future decompensation in advanced chronic liver disease( ACLD) patients.

This study was therefore designed to a)estimate the presence of liver parenchymal inflammation in patients with diagnosed compensated advanced chronic liver disease along with small gut bowel inflammation to determine the incidence of decompensation in such patients as risk factors, b) Using machine learning to develop a model for predictability to triage patients with near likelihood of decompensation.

## **Methods**

61 patients of compensated advanced chronic liver disease (cACLD) with no prior history of hepatitis infection were enrolled in the study after informed consent. Approval was obtained from the local institutional review board (Adv/L2/02.2) Patient demographics were recorded along with a history of prior alcohol intake, diabetes mellitus. Any patient with a past history of ascites, upper gastro intestinal bleed or recent encephalopathy was excluded from the study. Ultrasound examination of the abdomen was done in all patients in fasting state followed by shear wave elastography on Aplio i 800 (Canon Japan). SWE was performed in a standardised manner with patient in left decubitus position. ROI 2x2 cm was placed 2 cm below the liver

capsule in segments 7,8 of right lobe and patient was told hold breath in mid inspiration. At least six readings were obtained and IQR/median of <30 was determined as a cut off for optimal readings. Patient was made to lie in supine position and similar procedure was repeated after focussing on the small gut loops with ROI being 1x1 cm in size and covering the small bowel wall. Again six readings of SWE and SWD were obtained and median value determined for SWD. Liver stiffness was categorised into F1-F4 stages observing rule of four with less than 5 kPa being normal. All patients with less than 13 kPa were excluded from study. SWD Value of less than 12 m/s/kHz for liver was the cut off for inflammation of liver while value of 11 m/s/kHz was the cut off for bowel wall. Mean liver stiffness (LSM), Shear wave dispersion of liver (SWD) was determined in the prescribed manner and the values recorded. This was followed by estimation of bowel inflammation using shear wave dispersion (SBD) of the wall of the small bowel (a value of <11 m/s /kHz was taken as normal). All patients were re-examined using the same imaging parameters and findings recorded at one, three and six-month interval or any time in that period of 90 days. Any history of any gastro intestinal bleed, ascites or encephalopathy during this period was clinically suspected as a sign of decompensation and also marked as the end point of the study for that particular patient (workflow Chart 1) Based on the elastographic findings, the patients were divided into four groups i.e. Group I(A0B1) patients had increased liver stiffness F4 on elastogram which was more than 13 kPa but with normal liver shear wave dispersion i.e. Less than 12 m/s/Khz and with raised SBD of >11 kPa. Group II(A1B0) had patients with raised LSM like in other groups but also with raised SWD in the liver >12 kPa but there was no inflammation in the small bowel wall. Group III (A1B1) also had raised LSM but also had raised SWD of liver as well as raised SBD of small bowel wall. Group IV(A0B0) had raised LSM alone with normal SWD and SBD.

All patients were asked to come for three follow-up evaluations using the same technique at 30,45 and 90 days and the findings recorded .Patients were told to report in this period any time if they developed ascites or had gastrointestinal bleeding or altered sensorium.

**Statistical analysis:** Was done using XISTAT Premium 1414(addinsoft.USA) for descriptive analysis of the observations and their distribution. Mean, median and standard deviation were calculated along with box plot charts of the SWE parameters. One way Anova test was done to determine the statistical significance of the differences between the groups, with p value <0.05 being statistically significant. Kaplan Meyer survival along with the percentage of decompensation and hazard ratios of the parameters were also calculated. Predictability was

determined by using a machine learning model using classification and regression with random forest techniques using 350 decision trees.

## RESULTS

The study comprised of 61 patients of cACLD of alcoholic and fatty liver etiology. The overall mean age group of patients was 48.2 years with no statistically significant difference in the age between all the groups of patients (table 1). There were 55 males and 16 females. Alcoholic liver disease was more common and was seen in 42 patients while non-alcoholic liver disease (NAFLD) was present in 19 patients. The mean BMI for all the groups was 24.8 Kg/m<sup>2</sup> (23.9-26.2 :95 CI) with no statistically significant differences between the four groups. No statistically significant difference was seen in the mean C- reactive protein levels between all the groups with a mean C- reactive protein level of 2.3 mg/dl. The mean LSM, SWD and SBD in group I (A0B1) patients were 33 kPa, 9.8 and 13.0 m/s/Khz respectively (Figure 1a,b). The LSM, SWD and SBD in groups II, III and IV were 24 kPa, 19.7, 9.2 m/s/Khz (Figure 2a-c), 31 kPa, 19.5, 16.2 m/s/Khz (Figure 3a-c) and 20 kPa, 9.6, 8.7 m/s/Khz (Figure 4a-c) respectively and are also enlisted in Bar plot diagram (Figure 5a). One way Anova test showed that the differences in SWD and SBD in the four groups were statistically significant,  $p < 0.001$ . Regression analysis showed R<sup>2</sup> of 0.52 and 0.69 for SWD and SBD with LSM (Figure 5b). Liver decompensation was seen in 12 patients, of which there was none in group I, 1 patient in group IV, while group III and group IV had 7 and 4 patients who decompensated (figure 5c). Kaplan Meyer survival plot analysis (Figure 6) showed that group III and group II patients had the highest incidence of decompensation of liver, i.e. 27 % and 24% respectively, while 13% incidence was seen in group IV patients (Figures 7a-c, 8a-c). Eight patients of decompensated liver had a history of alcohol intake while 4 were those with NAFLD. The calculated hazard ratio SWD and SBD for decompensation in Groups I- III were 1:0.77, 1:2.44, (both were statistically insignificant), while for group III it was 1:24.4 (p value 0.03). The mean LSM Group III patients was 28 kPa, SWD was 18.2 m/s /Khz while SBD was 15.3 m/s/Khz. Based on the above findings, a machine-learning based predictive model was developed using classification and regression with random forest techniques with random sampling and replacement techniques. The number of decision trees used was 350. The model used an out of bag (OOB) confusion matrix sample and achieved a 75.4 % percentage predictability using SWD, SBD parameters to suggest the likelihood of liver decompensation over a 90-day period (Figure 9a,b). The most predictable variable in the

presence of increased liver SWD was SBD with mean decreased accuracy of 2.1. The model also showed a low OOB misclassification score, which was 0.279. The AUC for both SWD and SBD was 0.68 in the present study (Figure 9c). Linear regression analysis showed a linear regression equation of probability of decompensation in our study with the following equation as below.

$$\text{Pr}(\text{DECOMP}=\text{N}) = 1 / (1 + \exp(- (3.976985 - 0.075339 * \text{SWD} - 0.093349 * \text{SBD})).$$

## **DISCUSSION:**

To assess the prognosis of advanced chronic liver disease patients, two classification systems are in use, i.e. Child Pugh (CTP) classification and Model for end stage liver disease (MELD) classification, both of which use various blood parameters like serum bilirubin, INR, serum creatinine values for MELD and serum albumin, serum bilirubin, prothrombin time, ascites, and encephalopathy for CTP classification (9-11). Although these classifications have not been evaluated for statistical accuracy, they have been found to be useful in assessing the prognosis and predict three-month mortality and survival triage patients for TIPS procedure and organ transplantation. The C-statistics for prediction of three month survival for MELD is 0.87 and for CTP is 0.84. None of these systems is able to predict decompensation in a cACLD patient and so far there have been no imaging tests for the same. Our study is unique in that it is for the first time it has been done using SW dispersion for both liver and small bowel as imaging biomarkers for inflammation in known cACLD patients. Jeong et al (12) in an earlier study showed that SWE was useful in both diagnosis and follow up of cACLD patients. Sugimoto et al. (13) showed that SWD significantly increased with the degree of liver inflammation and was useful in the detection of the same. They showed that using a cut-off value of 8.5 (m/s)/kHz, SWD showed a very high accuracy in identifying the presence of lobular inflammation with an AUC of 0.95 in patients with NASH; however we used a cut off value of 13 m/s/kHz in our study. Earlier the authors of this study (14) also showed that SWD was a sensitive tool to evaluate inflammatory bowel diseases and can discriminate between various etiologies with good accuracy in the detection of bowel inflammation. Based on the premise that the presence of gut inflammation in patients with alcoholic and NAFLD patients is a common trigger factor for decompensation (15), the present study combines SWD of the liver with that of the small bowel as a two-step method for detection of inflammation in CACLD patients. Findings in our study suggest that there is concurrent low level

inflammation in the liver due to either direct insult by ingestion of alcohol or due to formation of dysmetabolic inflammatory markers formation which cause concurrent systemic and immune dysregulation as was seen in groups II and III patients who constituted 72.1% of patients. Any factor which accelerates the liver inflammation further like the presence of small bowel inflammation or an alcohol binge act as a second trigger to this dysimmune state leading to decompensation. Similar results were shown by Gianelli et al. (15) recently and proposed that it is the systemic inflammation and immune system dysregulation which are involved in the progression of disease and also initiate the decompensation stage of ACLD. Our study shows that patients of compensated ACLD can be phenotyped into four groups as shown above based on the presence of base line organ inflammation detected in the liver and small gut in the cACLD stage. We observed statistically significant differences in the degree of inflammation in the liver and also in the small bowel between these groups. Group I and IV patients with absent small bowel inflammation showed the least decompensation in a period of three months. There was only one patient in group IV who was alcoholic and had a binge intake of alcohol. The group III patients had the highest incidence of decompensation of liver, i.e. 27%, and had raised SWD and SBD. Group II patients had liver inflammation only and also showed decompensation of 24%. The mean SWD of both groups was high and comparable i.e. 19.7 and 19.5 db/ms/sec, which was statistically higher than other groups which showed no inflammation.

Shi et al (16) also observed in their study that patients with ACLF were a heterogenous population based on hepatic insults and extra hepatic insults, thus suggesting a twin etiology of deterioration of liver function. In patients with cACLD, ligands released from necrotic hepatocytes, known as damage associated molecular patterns (DAMPs) activate the immune system and cause a baseline low grade sterile systemic and organ inflammation – a process which causes increased SWD of liver as was seen in group II and group III patients in this study(17). The second pathway comprises pathogen associated molecular patterns(PAMPs) due to bacterial translocation from the gut due to portal hypertension and leaky gut resulting in local gut wall inflammation and ultimately accelerating the basal systemic inflammation by releasing pro-inflammatory cytokines(18-20). Studies have shown an altered immune system compensates for advanced chronic liver disease patients with diminished synthesis of innate immune system proteins and Toll-like receptors, together with reducing the bactericidal capacity of the stellate cells, neutrophils, natural killers, and macrophages, which makes these patients more prone to infections (21-22). Our study also showed that in group III patients it

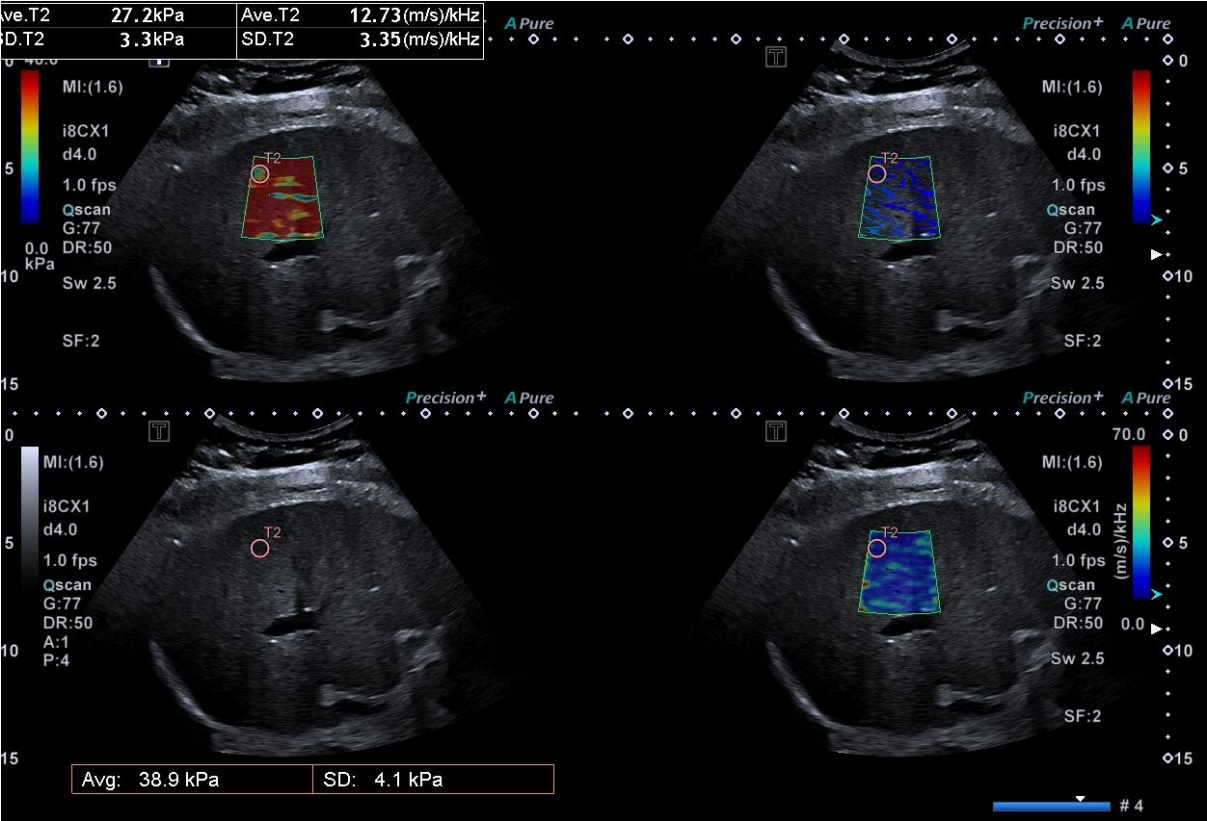
was the presence of coexisting raised SBD which resulted in an increase in the number of decompensated ACLD patients in this group. Our study hypothesizes that liver decompensation is a twin hit process where, at first, there is subclinical liver inflammation and progressive hepatocyte damage occurring due to release of DAMPS. With the altered immune status and other on-going hemodynamic changes of portal circulation, the small bowel becomes leaky which leads to release of PAMPS which after a certain threshold results in decompensation. The prediction model developed using machine learning random forest model of classification in the study showed a 75% accuracy with SWD and SBD variables with latter being an important factor with a minimum decreased accuracy of 2.1 in patients with raised SWD. The determination of SBD increased the hazards ratio to 1:24.4 for group III patients, while for SWD alone it was 1:2.4. These observations suggest that both these imaging biomarkers play an important role in the conversion of a compensated ACLD patient to a decompensated ACLD patient with a high SBD being the most important factor. Our study showed that no significant difference in the CRP levels between the groups and thus did not have much predictive value in suggesting decompensation. We did not use other sophisticated inflammatory markers like Interleukines, tumor necrosis factor for our study. While CRP is an indirect marker for system inflammation and can be elevated in any etiology causing inflammation, it was not of value in our cases as they were all in a compensated stage with ongoing indolent liver and small bowel inflammation in groups I-III. Serum ALT levels also have been shown to have no direct correlation with liver inflammation and in a study by Ferraioli et al. (23) patients with raised SWD had normal ALT values which was also the case in all the four groups of the study.

Our study highlights that SWE has the potential to determine not only liver stiffness but when shear wave dispersion is used along with, it can quantify liver and small bowel inflammation which have a high (75%) predictive value to suggest a short term likelihood of decompensation of the liver.

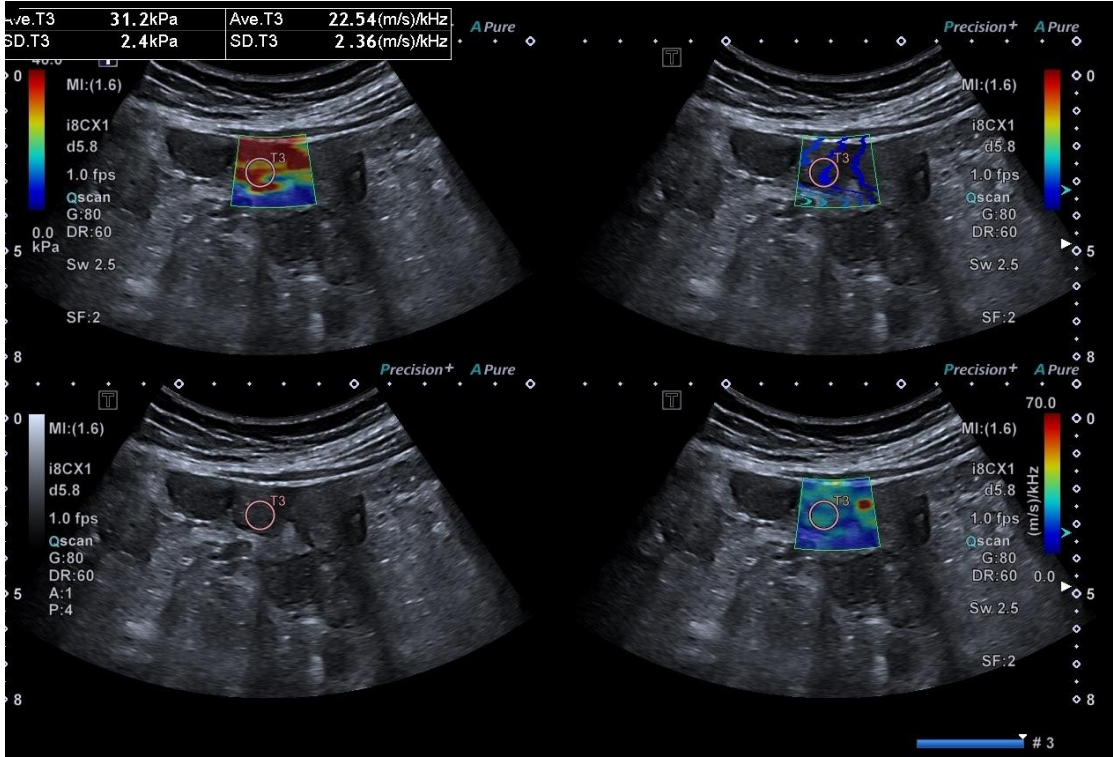
**CONCLUSION:** Our study shows that all other prognostic models have been of value in decompensated chronic liver disease patients for short and long term mortality or have been used to time the organ transplantation. The use of SWE markers is a novel way to evaluate patients with cACLD not only for diagnosis but can also be of help to prognosticate these patients for three month likelihood of decompensation and necessary management measures can be taken to prevent it.



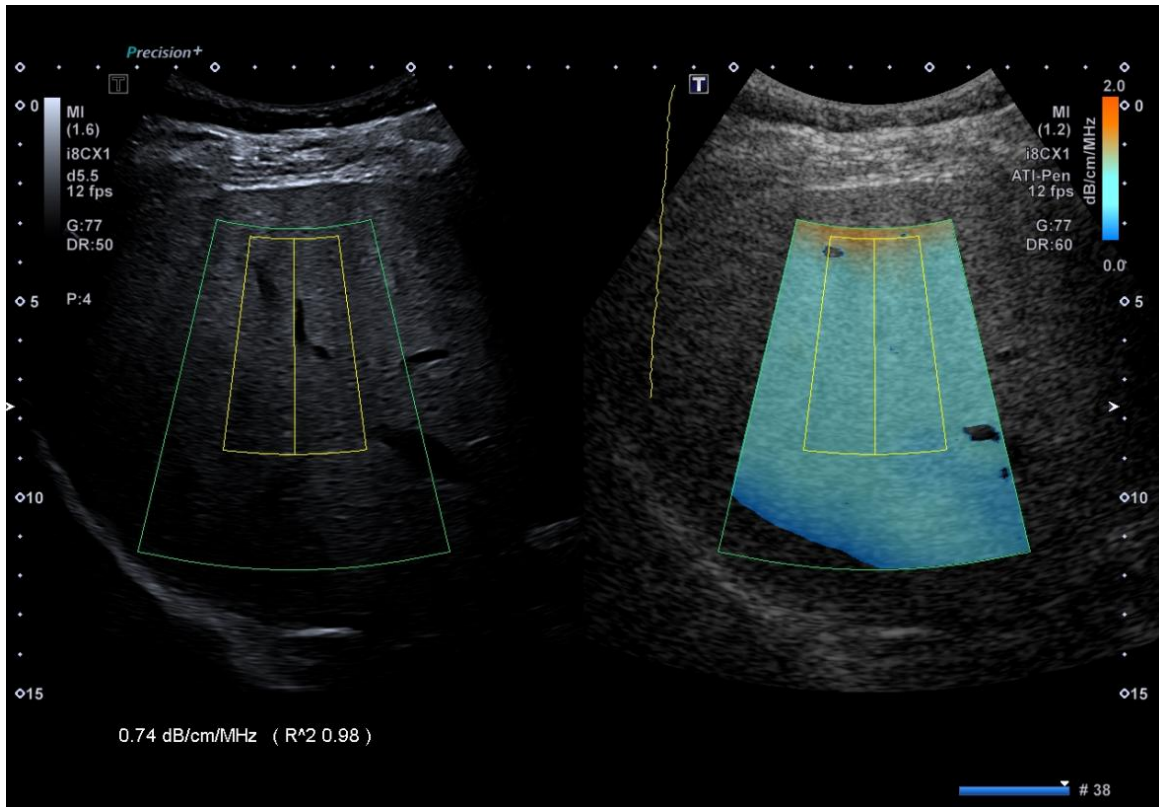
**Figures and legends:**



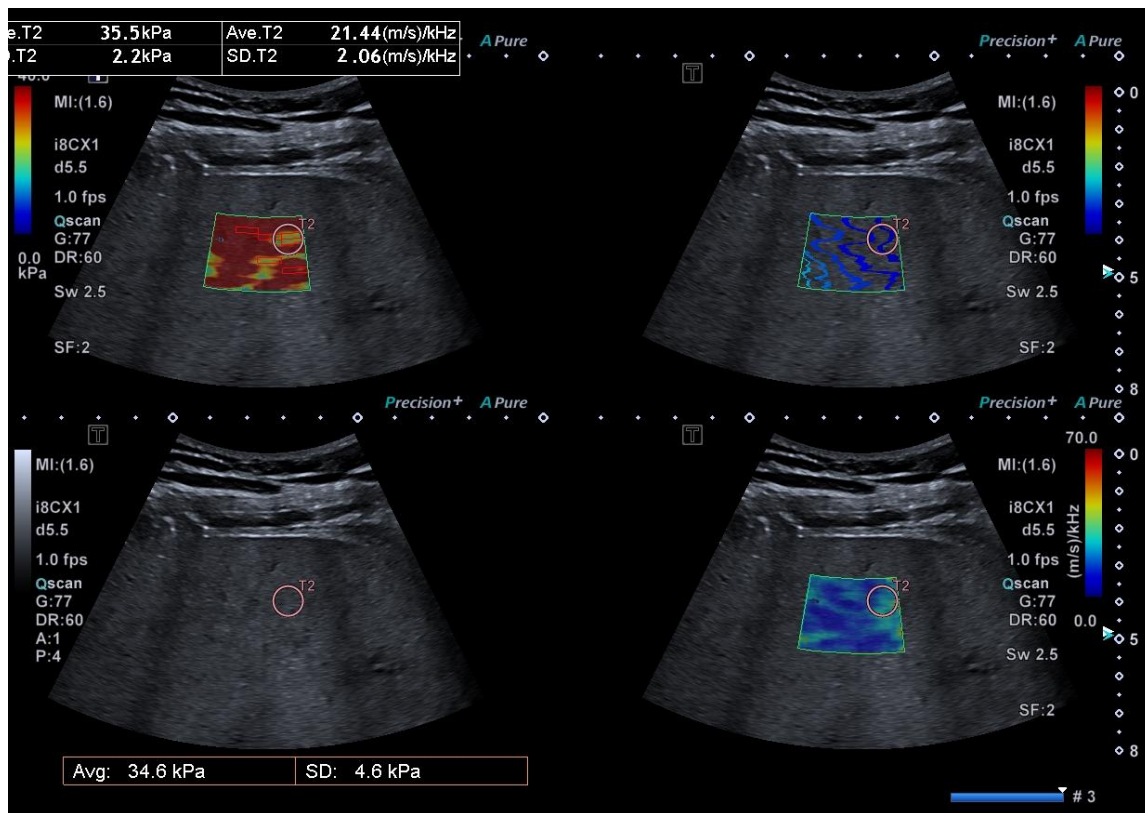
**Figure 1: a)** Group I (A0B1) patient showing shear wave elastogram with liver stiffness of 27.2 kPa and Shear wave dispersion of 12.7m/s/kHz



**Figure 1 b)** Shear wave elastogram of the small bowel showing increased dispersion of 22.5 m/s/kHz.



**Figure 2: a)** Group II(A1B0) patient with fatty liver with ATI of 0.74dB/cm/MHz .



**Figure 2b)** Shear wave elastogram of liver showing increased liver stiffness 35 kPa and increased shear wave dispersion of 21.4 m/s/kHz

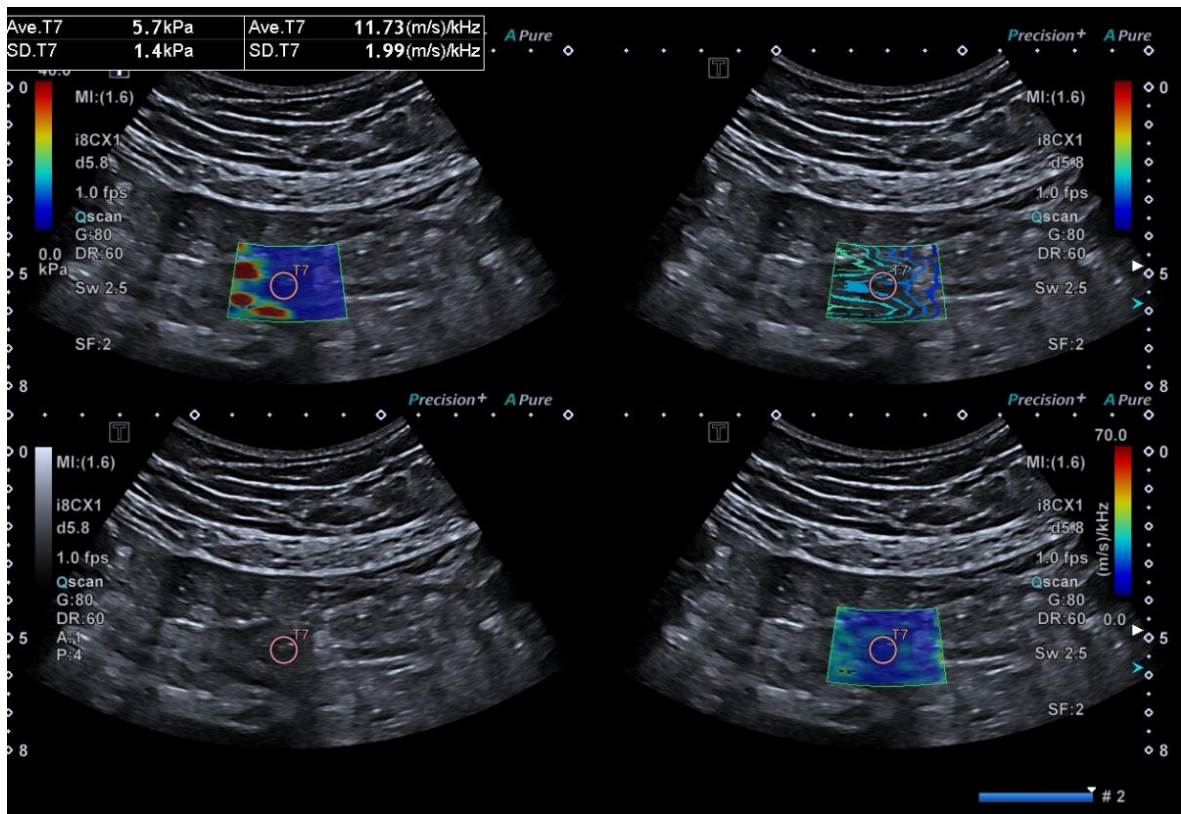


Figure 2 c) Elastogram of the small bowel wall showing normal dispersion of 11.7 m/s/kHz.

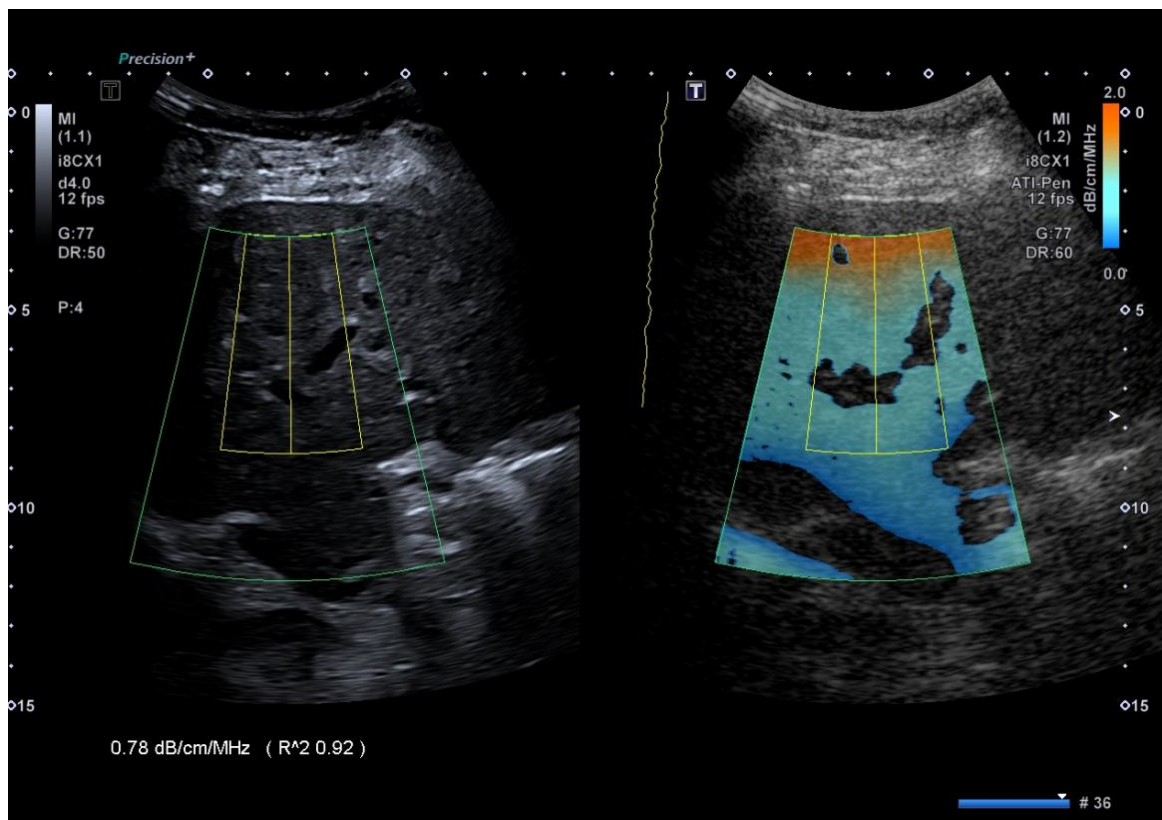
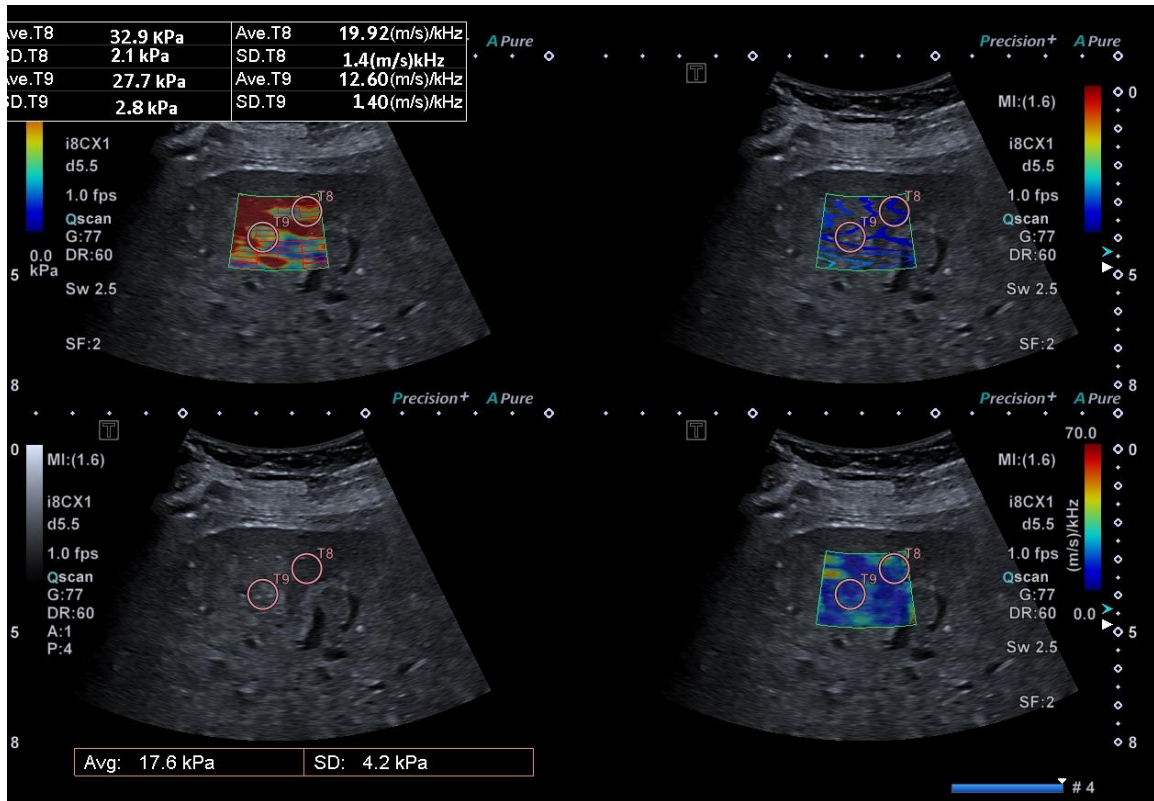
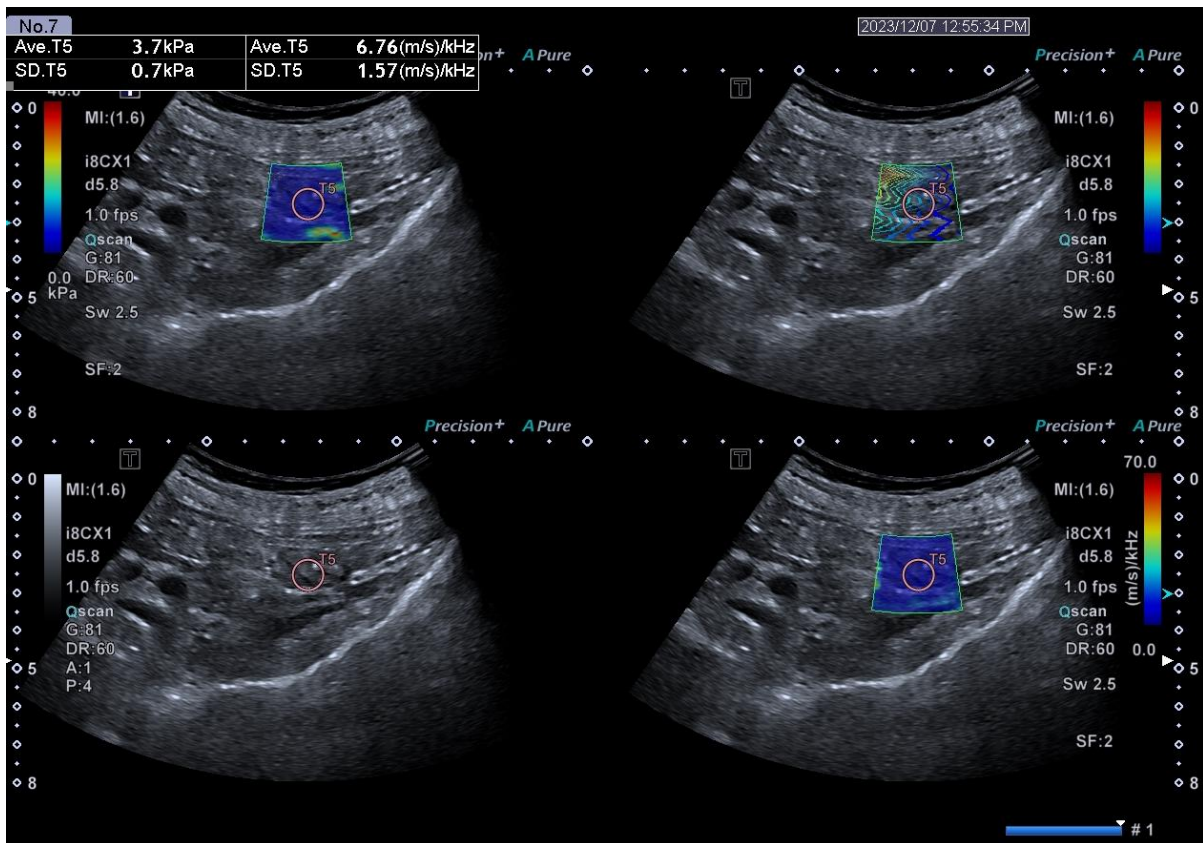


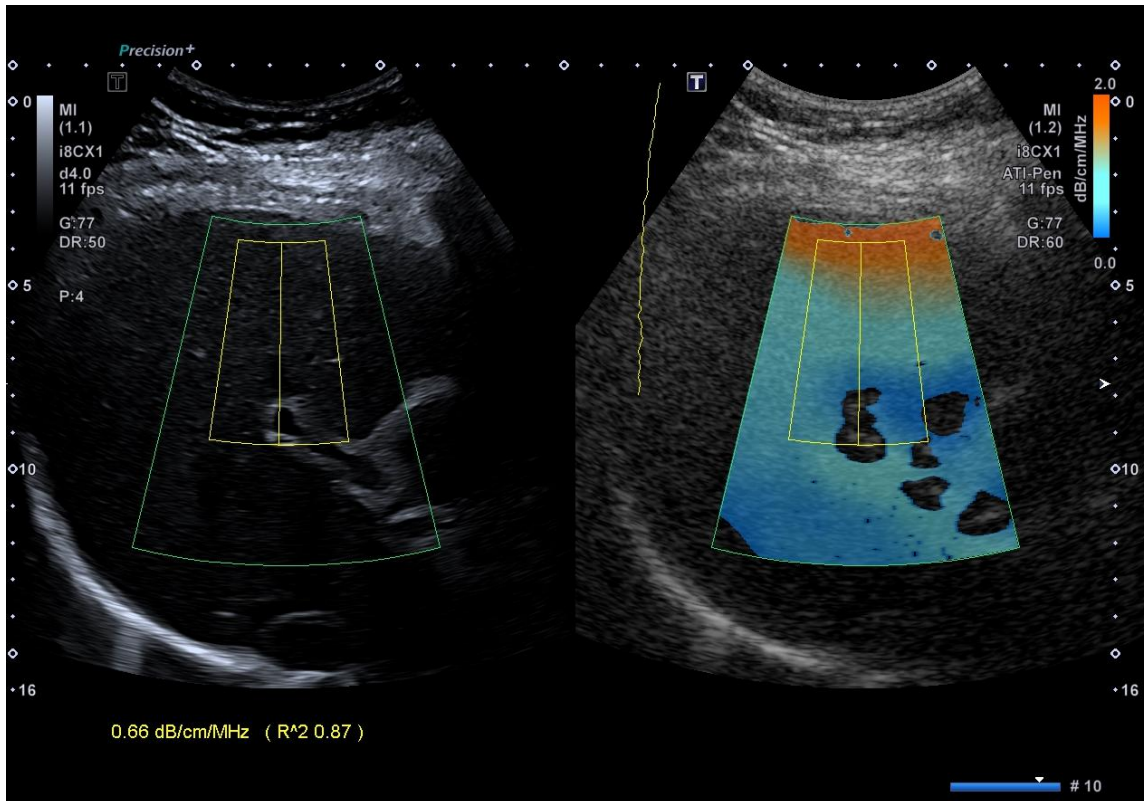
Figure 3: a) Ultrasound grey scale image of Group II (A1BO) alcoholic patient showing ascites with coarse liver



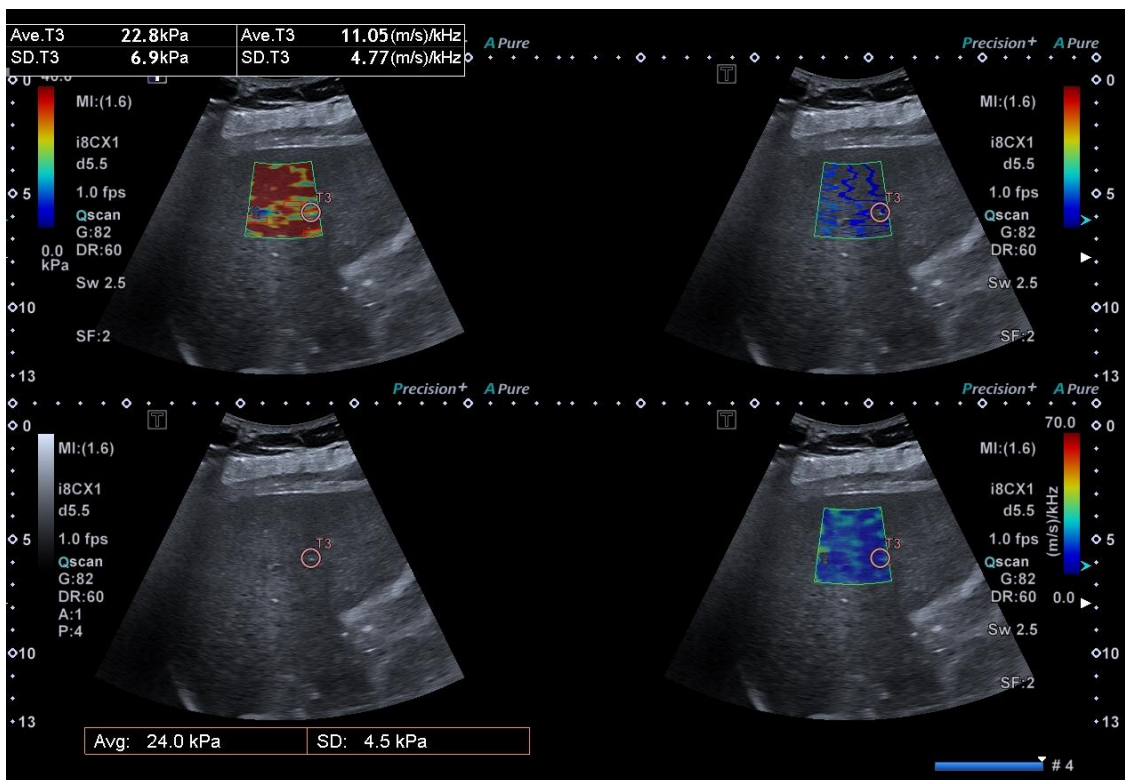
**Figure 3.b)** SW elastogram of liver with increased maximum liver stiffness 32.9 Kpa and increased maximum dispersion of 19.9 m/s/kHz.



**Figure 3c)** SW elastogram of small bowel showing normal dispersion of 6.7 m/s/kHz



**Figure 4 a)** Group III(A1B1) female patient with NAFLD with increased liver fat with ATI of 0.66 db/cm/MHz.



**Figure 4 b)** SW elastogram of liver showing increased stiffness of 32 kPa and increased dispersion of 19.9 m/s/KHz

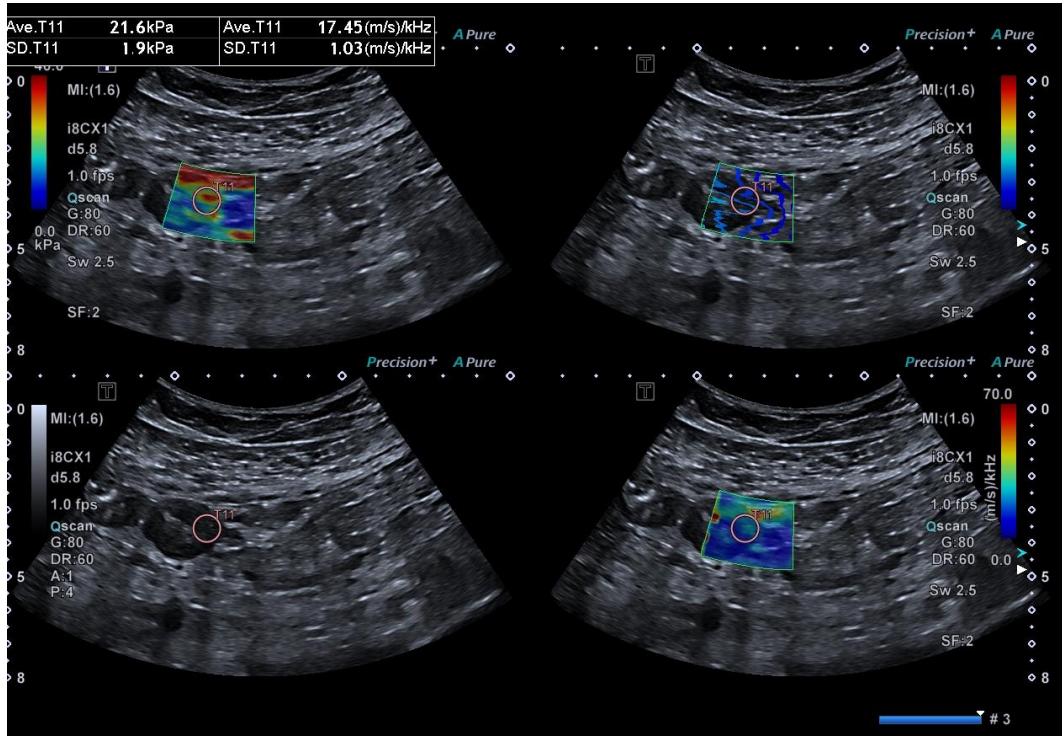


Figure 4c) Bowel wall showing increased dispersion of 17.45 m/s/kHz

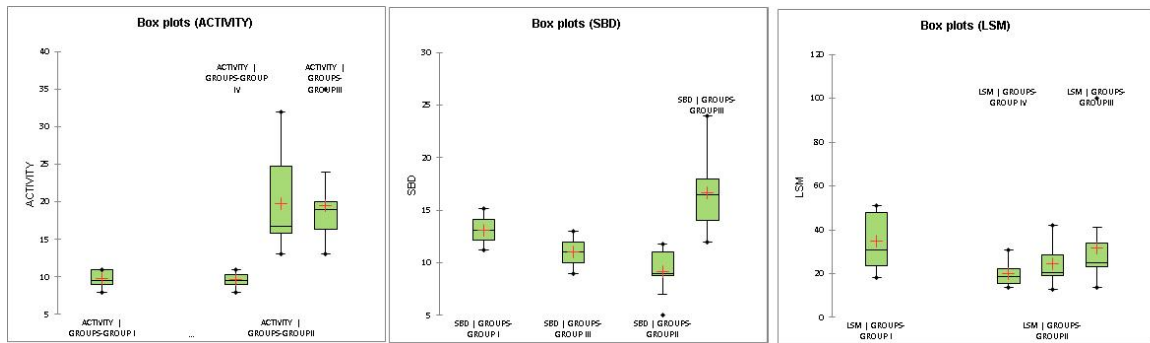
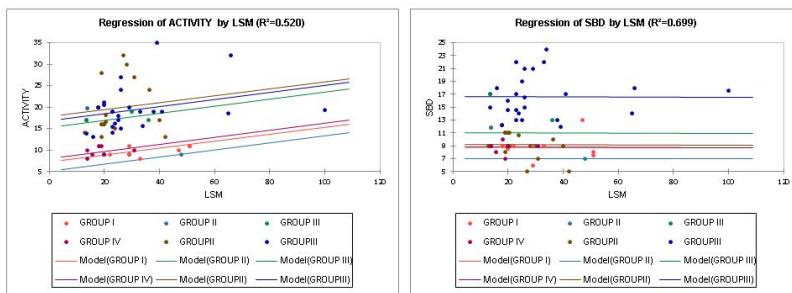


Figure 5a: Box plots showing distribution of SWE parameters in the different groups of Cirrhosis patients.



Model parameters (ACTIVITY):							Model parameters (SBD):								
Source	Value	Standard error	t	Pr >  t	Lower bound	Upper bound	p-values significant	Source	Value	Standard error	t	Pr >  t	Lower bound	Upper bound	p-values significant
Intercept	16.910	1.660	10.184	<0.0001	13.581	20.239	***	Intercept	16.680	0.928	17.977	<0.0001	14.819	18.540	***
LSM	0.082	0.043	1.897	0.063	-0.005	0.169	.	LSM	-0.001	0.024	-0.041	0.967	-0.049	0.047	o
GROUPS-GROUP I	-9.764	1.837	-5.316	<0.0001	-13.447	-6.082	***	GROUPS-GROUP I	-7.868	1.026	-7.666	<0.0001	-9.926	-5.811	***
GROUPS-GROUP II	-11.844	4.866	-2.434	0.018	-21.601	-2.088	*	GROUPS-GROUP II	-9.632	2.719	-3.542	0.001	-15.084	-4.180	***
GROUPS-GROUP III	-1.615	3.470	-0.465	0.644	-8.571	-1.989	.	GROUPS-GROUP III	-5.647	1.939	-2.912	0.005	-9.534	-1.759	**
GROUPS-GROUP IV	-8.928	1.982	-4.506	<0.0001	-12.901	-4.955	***	GROUPS-GROUP IV	-7.910	1.107	-7.143	<0.0001	-10.130	-5.689	***

Significance codes: 0 <\*\*\*<0.001< \*\*<0.01< \*<0.05< .<0.1<.<1

Figure 5 b: ANOVA with regression plots of SWD and SBD with LSM in different ACLD groups.

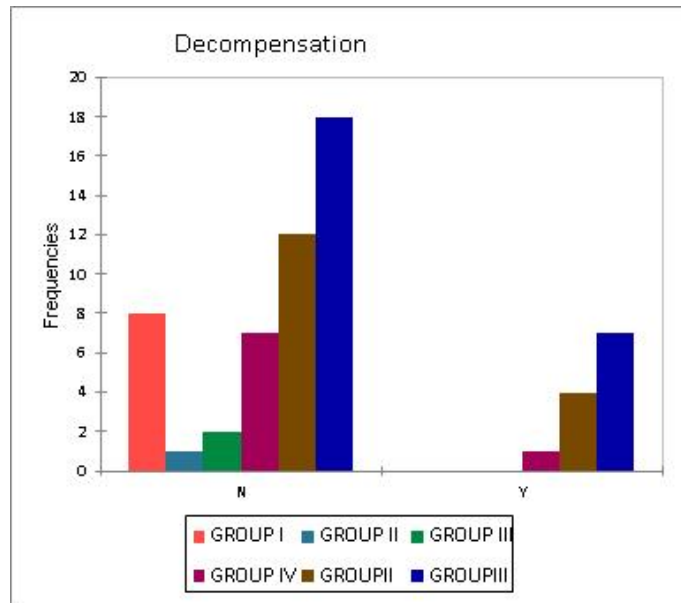


Figure 5 c: Frequency bar diagram of decompensation in different cACLD groups.

**Survival proportions in percentages**

Days	Group I	Group II	GroupIII	Group IV
0.000	100.000	100.000	100.000	100.000
30.000			96.296	
45.000		94.118	88.889	
60.000			85.185	87.500
90.000	100.000	76.471	74.074	87.500

**Graphics of survival proportions: of compensation**

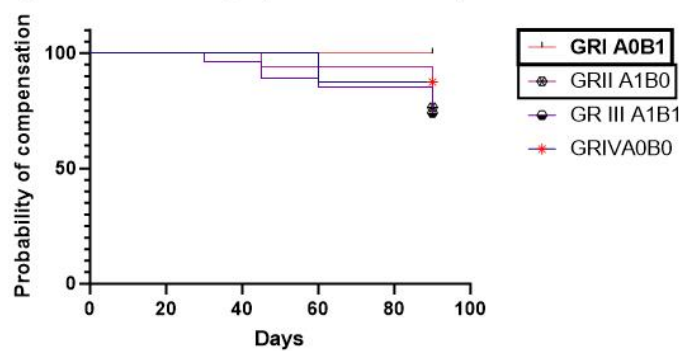
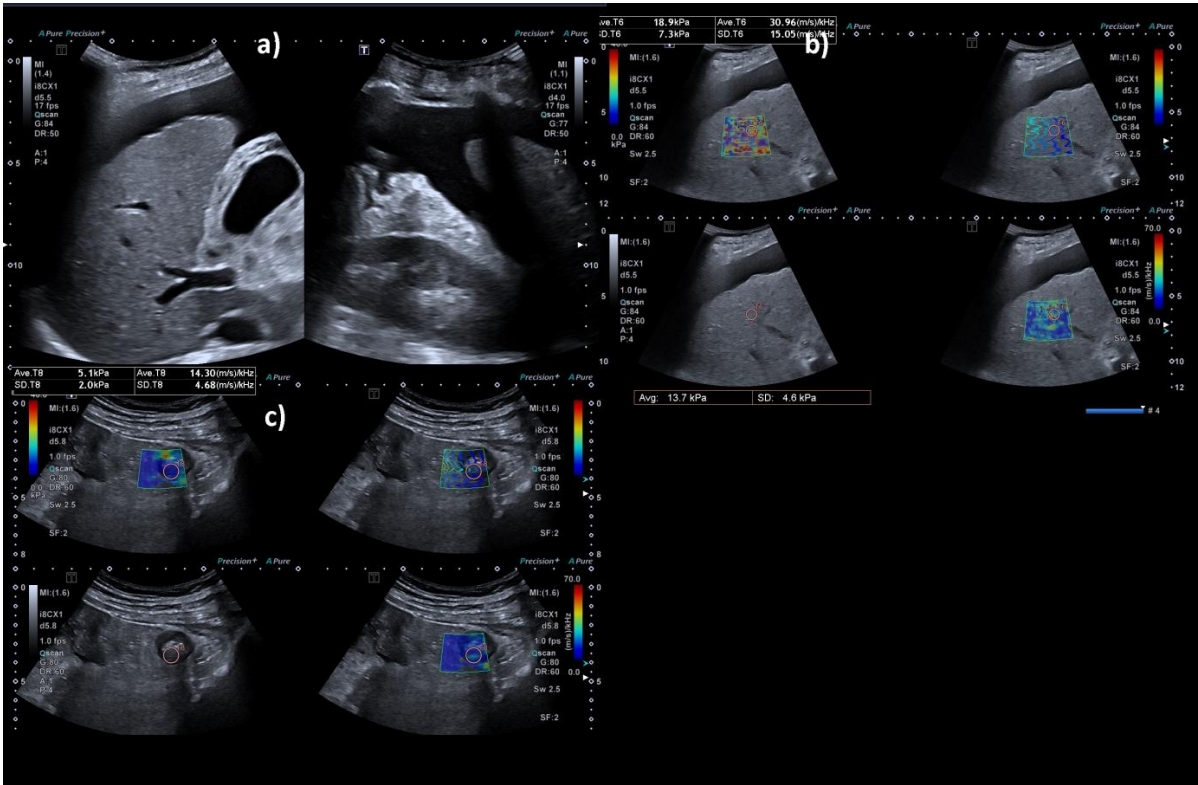
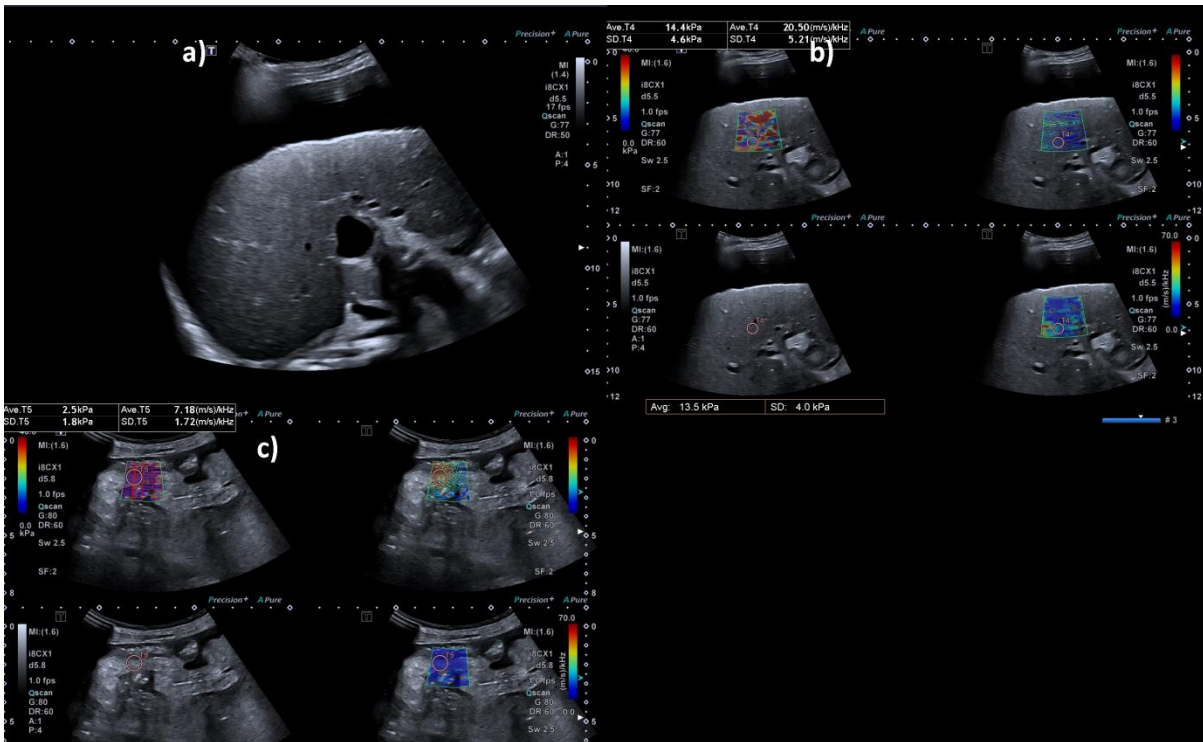


Figure 6: Graph showing Kaplan Meyer and percentage decompensation survivor plot in Cirrhotic groups of patients.

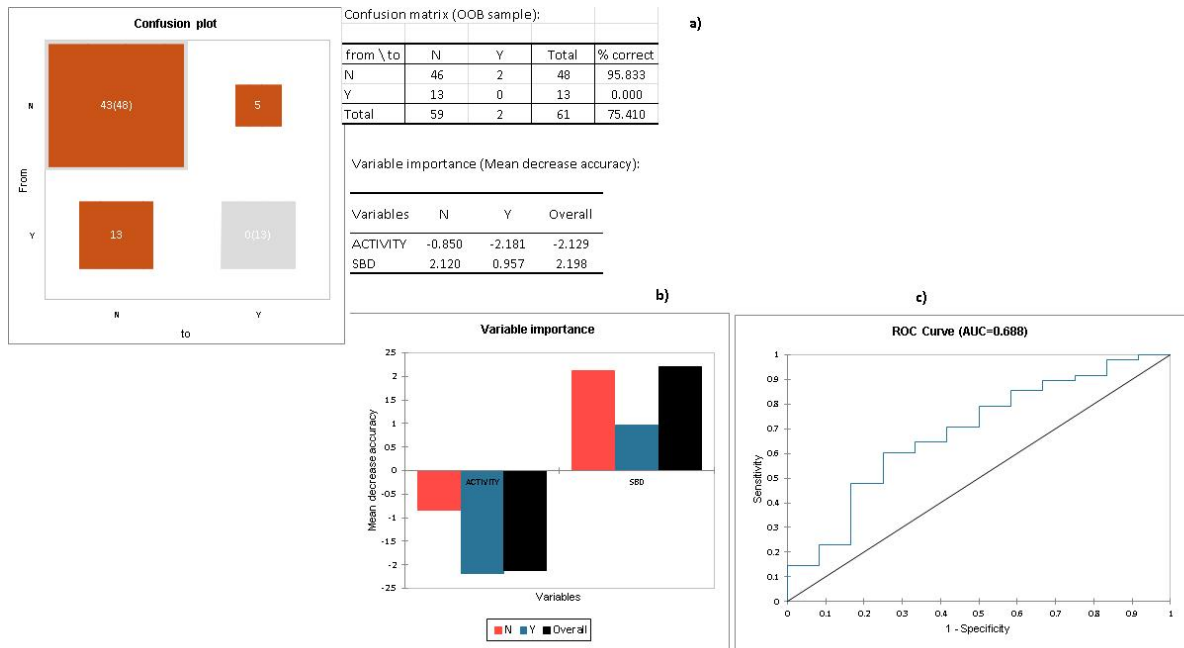


**Figure 7: a-c)** Follow up Ultrasound at 50 days of a group III patient showing ascites with cirrhosis liver. b) SW elastogram with increased liver stiffness 18 kPa and increased inflammation with dispersion of 30.9 m/s/kHz. c) SW elastogram of small bowel showing increased dispersion of 14 m/s/kHz



**Figure 8 a-c; a)** Group IV (A0B0) patient with ascites and shrunken liver b,c)SWE image of the same patient with increased liver stiffness and normal liver dispersion and SBD.



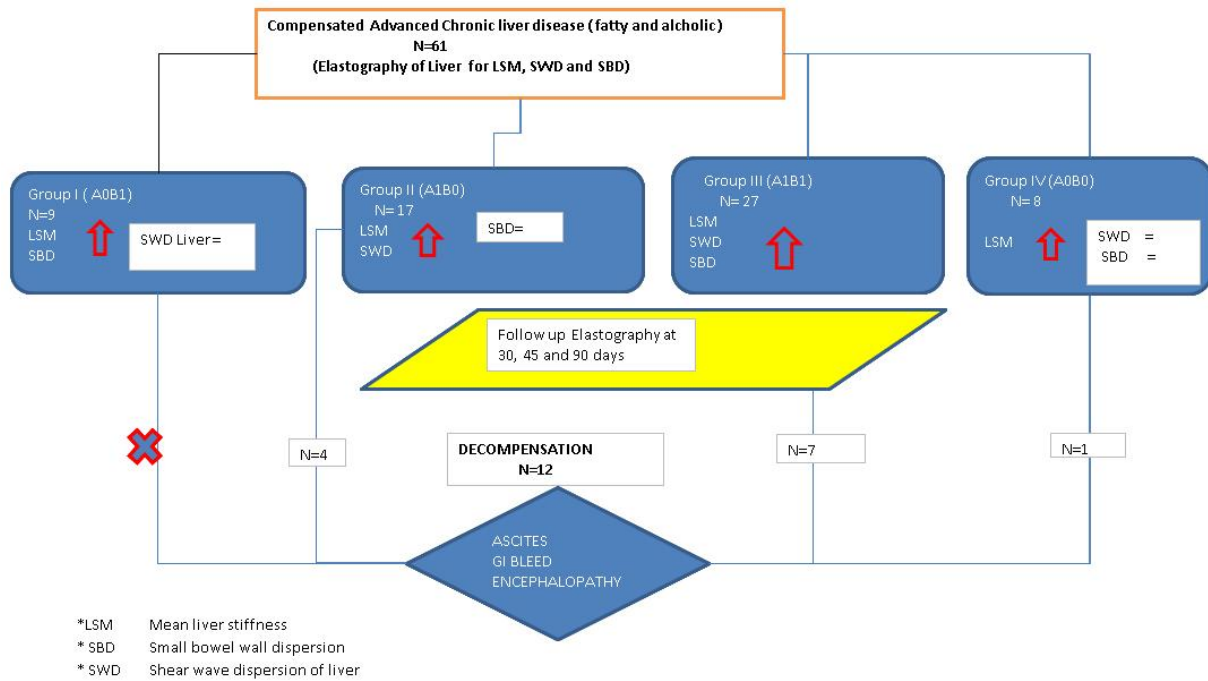


**Figure 9:** a,b) Confusion plot with confusion matrix using the random forest classification c) AUC plot of the SWD and SBD variables.

**Table 1:** Patient Demographics

PATIENT DEMOGRAPHICS						
SNO.	PARAMETER	GR I (A0B1)	GR II (A1B0)	GR III(A1B1)	GR IV (A0B0)	p value
1	Mean Age	48.8	48	49.2	49.5	>0.05
2	Sex					
a)	Males	5	12	21	7	NS
b)	Females	4	5	6	1	NS
3	Number of patients	9	17	27	8	*
4	ALCOHOL	5	12	19	6	NS
5	NAFLD	4	5	8	2	NS
6	Diabetes	3	11	12	4	NS
7	CRP	2.5	2.8	3.8	1.9	<0.01
8	BMI	24.4	26.2	25.1	25.8	NS
9	LSM	33	24	31	20	<0.001
10	SWD	9.8	19.6	19.2	9.6	<0.001
11	SBD	12.2	9.2	16.4	8.7	<0.001

NAFLD: Non alcoholic fatty liver disease, CRP : C-reactive protein, BMI: body mass index  
 LSM: mean liver stiffness, SWD: shear wave dispersion, SBD: smallbowel wall dispersion



**Chart 1:** Work flow Diagram of the evaluation of compensated advanced chronic liver disease patients.

## REFERENCES:

- [1] Mas VR, Fassnacht R, Archer KJ, Maluf D. Molecular mechanisms involved in the interaction effects of alcohol and hepatitis C virus in liver cirrhosis. *Mol Med* 2010; 16: 287-297 [PMID: 20386865 DOI: 10.2119/molmed.2009.00165].
- [2] Weiskirchen R, Tacke F. Cellular and molecular functions of hepatic stellate cells in inflammatory responses and liver immunology. *Hepatobiliary Surg Nutr* 2014; 3: 344-363 [PMID: 25568859 DOI: 10.3978/j.issn.2304-3881.2014.11.03].
- [3] Asrani SK, Kamath PS. Natural history of cirrhosis. *Curr Gastroenterol Rep* 2013; 15: 308 [PMID: 23314828 DOI: 10.1007/s11894-012-0308-y].
- [4] Albillos A, Lario M, Álvarez-Mon M. Cirrhosis-associated immune dysfunction: distinctive features and clinical relevance. *J Hepatol* 2014; 61: 1385-1396 [PMID: 25135860 DOI: 10.1016/j.jhep.2014.08.010].
- [5] Arroyo V, García-Martínez R, Salvatella X. Human serum albumin, systemic inflammation, and cirrhosis. *J Hepatol* 2014; 61: 396-407 [PMID: 24751830 DOI: 10.1016/j.jhep.2014.04.012].

- [6] Sugimoto, K.; Moriyasu, F.; Oshiro, H.; Takeuchi, H.; Yoshimasu, Y.; Kasai, Y.; Itoi, T. Clinical Utilization of ShearWave Dispersion Imaging in Diffuse Liver Disease. *Ultrasonography* 2020, 39, 3–10.
- [7] Jeong, J.Y.; Cho, Y.S.; Sohn, J.H. Role of Two-Dimensional Shear Wave Elastography in Chronic Liver Diseases: A Narrative Review. *World J. Gastroenterol.* 2018, 24, 3849–3860.
- [8] Claria J, Stauber RE, Coenraad MJ, Moreau R, Jalan R, Pavesi M, et al. Systemic inflammation in decompensated cirrhosis: characterization and role in acute-on-chronic liver failure. *Hepatology* 2016;64:1249–1264.
- [9] Child C, Turcotte J. Surgery and portal hypertension. In: Child CG, ed. *The Liver and Portal Hypertension*. Philadelphia: Saunders, 1964:50.
- [10] Christensen E, Schlichting P, Fauerholdt L, Gluud C, Anderson P, Juhl E, Poulson H, et al. Prognostic value of Child-Turcotte criteria in medically treated cirrhosis. *HEPATOLOGY* 1984;4:430-435.
- [11] Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. *HEPATOLOGY* 2000;31:864-871.
- [12] Jeong, J.Y.; Cho, Y.S.; Sohn, J.H. Role of Two-Dimensional Shear Wave Elastography in Chronic Liver Diseases: A Narrative Review. *World J. Gastroenterol.* 2018, 24, 3849–3860
- [13] Sugimoto, K.; Moriyasu, F.; Oshiro, H.; Takeuchi, H.; Yoshimasu, Y.; Kasai, Y.; Itoi, T. Clinical Utilization of ShearWave Dispersion Imaging in Diffuse Liver Disease. *Ultrasonography* 2020, 39, 3–10
- [14] Giannelli V, Di Gregorio V, Iebba V, Giusto M, Schippa S, Merli M, Thalheimer U. Microbiota and the gut-liver axis: bacterial translocation, inflammation and infection in cirrhosis. *World J Gastroenterol* 2014; 20: 16795-16810 [PMID: 25492994 DOI:10.3748/wjg.v20.i45.16795].
- [15] Kapoor A, Singh A, kapur A, Mahajan G, Sharma S. Use of shear wave imaging with intestinal ultrasonography in patients with chronic diarrhea. *J of clinical ultrasound* 2023; 1-13. <https://doi.org/10.1002/jcu.23594>

- [16] Shi Y, Yang Y, Hu Y, Wu W, Yang Q, Zheng M, Zhang S, Xu Z, Wu Y, Yan H, Chen Z. Acute-on-chronic liver failure precipitated by hepatic injury is distinct from that precipitated by extrahepatic insults. *Hepatology* 2015; 62: 232-242 [PMID: 25800029 DOI:10.1002/hep.27795]
- [17] Tiegs G, Lohse AW. Immune tolerance: what is unique about the liver. *J Autoimmun* 2010; 34: 1-6 [PMID: 19717280 DOI: 10.1016/j.jaut.2009.08.008.
- [18] Ilan Y. Leaky gut and the liver: a role for bacterial translocation in nonalcoholic steatohepatitis. *World J Gastroenterol* 2012; 18:2609-2618 [PMID: 22690069 DOI: 10.3748/wjg.v18.i21.2609].
- [19] Lutz P, Nischalke HD, Strassburg CP, Spengler U. Spontaneous bacterial peritonitis: The clinical challenge of a leaky gut and a cirrhotic liver. *World J Hepatol* 2015; 7: 304-314 [PMID:25848460 DOI: 10.4254/wjh.v7.i3.304].
- [20] Fukui H. Gut-liver axis in liver cirrhosis: How to manage leaky gut and endotoxemia. *World J Hepatol* 2015; 7: 425-442 [PMID: 25848468 DOI: 10.4254/wjh.v7.i3.425].
- [21] Aoyama T, Paik YH, Seki E. Toll-like receptor signaling and liver fibrosis. *Gastroenterol Res Pract* 2010; 2010: pii: 192543 [PMID: 20706677 DOI: 10.1155/2010/192543]
- [22] Nakamoto N, Kanai T. Role of toll-like receptors in immune activation and tolerance in the liver. *Front Immunol* 2014; 5: 221[PMID: 24904576 DOI: 10.3389/fimmu.2014.00221].
- [23] Ferraioli, G.; Maiocchi, L.; Dellafiore, C.; Tinelli, C.; Above, E.; Filice, C. Performance and Cutoffs for Liver Fibrosis Staging of aTwo-Dimensional Shear Wave Elastography Technique. *Eur. J. Gastroenterol. Hepatol.* 2021, 33, 89–95.