

The Clinical Utility of Transient Elastography (TE) in Predicting Clinical Outcomes and Decompensation in Cirrhosis

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Abstract

Background: Transient Elastography (TE) is a non-invasive method providing reliable measurements help staging liver fibrosis which is crucial for both prognosis and management. In this study, we assess the utility of TE in predicting clinical outcomes.

Methods: Retrospective cohort 272 patients underwent serial TE measurements in a single liver center. TE scores at baseline and longitudinal change over time were correlated with the primary outcome of clinical decompensation (ascites, encephalopathy, variceal bleed, increase in CPC > 2, HCC, liver transplant, and death).

Results: 162 patients (62%) had an initial TE score of <12.5 kPa (non-cirrhotic) and 100 patients (38%) had a TE score of >12.5 kPa consistent with cirrhosis. In the cirrhosis group, mean TE score 26.4 kPa compared to 7.0 kPa non-cirrhosis ($p < 0.0001$). In the cirrhotic group, 85% had esophageal varices on upper endoscopy that had baseline TE score of ≥ 21.0 kPa in compare to 13% with baseline TE scores 12.5-20.0kPa ($p < 0.05$). During a median follow-up period of 4.5 years, 14% of patients achieved a primary outcome of clinical decompensation [30% cirrhosis versus 4% non-cirrhosis ($p < 0.01$)]. Logistic regression analysis demonstrates that TE score of ≥ 35 kPa was the strongest predictor for primary endpoint OR 6.5 (95% CI 8.2 – 4.8, $p < 0.01$). An Annual increase in TE score of ≥ 8 kPa to the cirrhotic range ≥ 12.5 kPa was associated with a significant OR 2.8 (95% CI 2.1-3.9, $p < 0.01$) for developing clinical decompensation.

Conclusion: Baseline TE scores ≥ 35 kPa & annual increment TE score ≥ 8 kPa were associated with a significant risk of clinical decomposition.

Key words: Transient elastography; liver fibrosis; Fibroscan; clinical decompensation;

ASMA- Anti-smooth muscle antibody

AFP- Alpha-fetoprotein

ALT- Alanine transaminase

AST- Aspartate transaminase

GGT- Gamma-glutamyl transferase

ALP-Alkaline phosphatase

MRE -Magnetic resonance elastography

PHG- Portal Hypertensive Gastropathy

HCC-Hepatocellular cancer

MELD- Model for End-Stage Liver Disease

CPC-Child Pugh Class

SD- Standard deviation

APRI – AST/platelets ratio

AUC/AUROC – Area under curve / Area under the receiver operator curve

ELF- Enhanced liver fibrosis

Introduction

The prevalence of liver disease has been increasing not only in the United States but also throughout the developed & developing world [1,2]. This is being driven by epidemics in viral hepatitis (B & C), Non-Alcoholic Steatohepatitis (NASH) and alcoholic liver disease. These liver diseases result in liver fibrosis that can progress to advanced fibrosis, cirrhosis, portal hypertension and liver failure [3]. Decompensation in liver diseases can lead to liver failure, cancer, and death.

The gold standard for identifying hepatic inflammation and fibrosis is a liver biopsy. However, procuring a liver biopsy has major disadvantages including 1) Invasive technique with the risk of bleeding and penetration especially in patients with cirrhosis.

Abbreviations

TE – Transient Elastography

NAFLD – Non-alcoholic fatty liver disease

NASH – Non-alcoholic steatohepatitis

ANA- Anti-nuclear antibody

AMA- Anti-mitochondrial antibody

2) Sampling error and inadequate sample size. 3) Inter-observer variations in interpretation [4]. These disadvantages have led to the development of non-invasive markers of liver fibrosis in the last decade. These include serum markers such as the APRI Score (AST/Platelets ratio), the Enhanced Liver Fibrosis test (ELF), vibration control imaging with Transient Elastography (TE) and Magnetic Resonance Elastography (MRE) [5,6,10,11,12]. These non-invasive tools can effectively identify liver fibrosis in the cross-sectional single read setting. Additionally, models such as the MELD score and Child-Pugh Class can prognosticate three-month mortality and surgical mortality respectively in these patients that demonstrate advanced fibrosis. Despite all this, we still do not have validated tools for predicting which patients will decompensate from their liver disease and experience significant morbidity based on non-invasive measurements of their fibrosis.

In this study, we use baseline and serial TE measurements in a heterogeneous group of patients at a single tertiary medical center to determine which patients are more likely to achieve the primary outcome of clinical decompensation (composite end-point including ascites, hepatic encephalopathy, variceal bleeding, an increase in Child-Pugh score >2 points, hepatocellular carcinoma, liver transplant, or death).

Methods

Clinical Assessment

Cirrhosis

Full clinical physical examination was conducted paying particular attention to the stigmata of chronic liver disease. The clinical diagnosis of cirrhosis was defined by the presence of any signs and symptoms of underlying liver disease including spider angiomas, palmar erythema, scleral icterus, jaundice, ascites, lower extremities edema and splenomegaly [7].

Clinical hepatic decompensation

These include hepatic encephalopathy, variceal hemorrhage, ascites, acute on chronic liver failure, hepatocellular cancer, liver transplantation and death [7].

Serological analysis

Laboratory investigation included routine blood tests, liver chemistry (ALT, AST, total bilirubin, ALP, GGT), AFP, coagulation panel, and full viral hepatitis panel. Furthermore, we also tested for markers autoimmune liver disease with ANA, AMA, ASMA, and Immunoglobulins levels.

Endoscopy

All patients underwent an endoscopic evaluation using adult size scope looking for signs of portal hypertension including evidence of varices (esophageal or gastric) as well as portal hypertensive gastropathy. The grading of esophageal varices from I-IV was done in accordance with the Paquet grading system [9].

Radiology Tests

All patients had a liver ultrasound within 6 months of transient elastography. Some patient had cross-sectional imaging with triple phase CT scan or MRI of the liver depending on the clinical indication. All studies were reviewed by an experienced radiologist.

Histopathology

Liver biopsies were carefully examined by two expert pathologists blinded for the TE results of patients. The histological diagnosis was established using Hematoxylin and Eosin (H & E) staining in addition to Masson's trichrome slides of formalin fixed paraffin-embedded liver tissue. The liver fibrosis was staged from 0 (no fibrosis), 1 (minimal fibrosis), 2 (moderate fibrosis), 3 (moderate to severe fibrosis), and 4 (advanced fibrosis/cirrhosis) [8].

Transient Elastography (TE) or Fibroscan®

All patients were fasting at least for four hours prior to obtaining the study. A standard protocol was used to conduct this procedure. The patient was placed in the supine position with the right arm elevated. The liver was percussed to find an optimal intercostal position for the probe. Using a standard probe, a 50 Hz ultrasound wave was introduced into the liver to gather measurements of shear wave velocity. A 2D-image and elastogram were evaluated for adequate transmission and positioning. Thirteen measurements were obtained from each patient according to the manufacturers' instructions (Fibroscan®, Echosens, France) yielding an overall median value with IQR <30% [21]. All patients underwent serial TE measurements with an interval of 6 to 12 months in accordance with their follow up schedules and clinical necessity deemed appropriate by their primary hepatologist [18,20,21].

Statistical Analysis

The clinical, radiological, endoscopic, and histopathological data were reported independently in a blinded fashion to eliminate bias. The results are displayed as the mean $\pm$ standard deviation of the sample or 95% confidence interval. The cohorts were compared using the ANOVA test with differences reported if $p < 0.05$. The diagnostic performance of each clinical test was determined using the area under the ROC curve (AUC). Established cut offs for each test were identified. [22] And confirmation attained through the extrapolation of ROC curves. These cut offs were used for the calculation of the sensitivity and specificity of each test. Unitarians and logistic regression analysis was performed in all patients to determine variables associated with liver biopsy staging and transient elastography. Logistic regression analysis was performed to identify factors associated with clinical decompensation. We looked at age, gender, ethnic origin, etiology, ALT, platelet count, albumin, Na-MELD score, and Child's Pugh Class

Patient Selection

A heterogeneous group of patients presenting to the Liver Center at Beth Israel Deaconess Medical Center (Boston, Massachusetts) were recruited into the study over a four and a half years period. The patient characteristics included a variety of liver diseases including chronic viral hepatitis, fatty liver disease and autoimmune liver disease (Table 1). This group also varied in the stage of liver disease including early fibrosis and scarring to cirrhosis. Comprehensive intake for each patient was done including clinical findings, serologies, transient elastography, and a histological assessment with liver biopsy. The study was approved by the committee on the clinical investigation at the Beth Israel Deaconess Medical Center with all patients giving informed consent prior to participation. A total of 358 patients were assessed for the study, of which 91 were excluded as their TE could not be obtained due to one of the following reasons: 1) Obesity resulting in excess abdominal wall fat (n= 62). 2) Narrow intercostal space (n=21). 3) Patient with massive ascites at the time of TE study (n=8). 4) Patients with incomplete transient elastography measurements (n=5). A total of 262 patients were finally included for assessment. Patients with a clinical diagnosis

of cirrhosis in whom liver biopsy confirming histological evidence of bridging fibrosis on Trichrome stain, radiological evidence of nodular liver on imaging with splenomegaly, and/or evidence of portal hypertension on endoscopic evaluation.

Results

272 patients enrolled in the initial analysis. Patient characteristics and demographic listed in (table 1). A total of 162 patients (62%) had an initial TE score of <12.5 kPa (non-cirrhotic) and 100 patients (38%) had a TE score of >12.5 kPa, consistent with cirrhosis irrespective of underlying disease. Mean TE score was 26.4 kPa (+/- 12.5 kPa SD) in the cirrhotic group compared to 7.0 kPa (+/- 2.5 kPa SD) in the non-cirrhotic group (p<0.0001). In the cirrhotic group, 36 patients (36%) had a baseline TE score between 12.5 – 20.0 kPa while 64 patients (64%) had a baseline TE score of ≥21.0 kPa. Of those 64 patients, 55 (85%) had esophageal varices on upper endoscopy compared to 5 out of 36 patients that had baseline TE scores of 12.5 to 20.0 kPa (p<0.05). The varices noted in the group of 5 patients mentioned above were no larger than grade I whereas the group of 55 patients with TE scores more than 21.0 kPa had varices graded I to IV figure 1.



Figure 1: Predictive ability of Transient Elastography (TE) to identify esophageal varices.

During a median follow up period of 4.5 years from the initial TE examination, 37 patients (14%) of total patients in the study achieved a primary composite endpoint of clinical decompensation. This included 30 patients in the cirrhotic group (30%) and 7 patients in the originally non-cirrhotic group (4%) that developed cirrhosis during the median follow up period as determined by serial TE measurements and clinical examination ($p<0.01$) figure 1.

In a sub-group analysis, 24 patients (24%) of the cirrhotic patients with an initial mean TE score of ≥ 21.0 kPa achieved primary composite endpoint whereas only 6 patients (6%)

with an initial TE score of 12.5 to 20.0 kPa experienced such an event ($P<0.05$). Logistic regression analysis was performed and demonstrates, TE score of >35 kPa was the strongest predictor of clinical decompensation based on initial TE score with an odds ratio (OR) of 6.5 (95% CI 8.2 – 4.8, $p<0.01$). We also looked at age, gender, ethnic background, etiology of liver disease, ALT, platelet count, albumin level, Na-MELD score, and Childs Pugh Class. The other factors that predicted clinical decompensation included Na-MELD ≥ 18 (OR) of 5.8 (95% CI 7.3 – 4.2, $p<0.01$), Childs Pugh Class C (OR) of 3.8 (95% CI 5.5 – 2.1, $p<0.01$). We also examined the relationship between the change in serial TE scores and

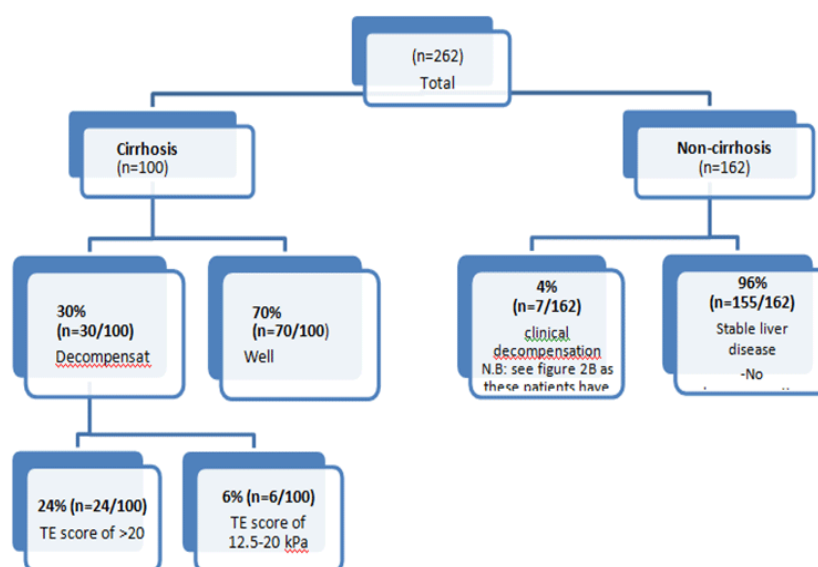


Figure 2A: The Initial Transient Elastography (TE) measurements in predicting clinical hepatic decompensation (ascites, hepatic encephalopathy, variceal bleeding, an increase in Child-Pugh score >2 points, hepatocellular carcinoma, liver transplant, or death)

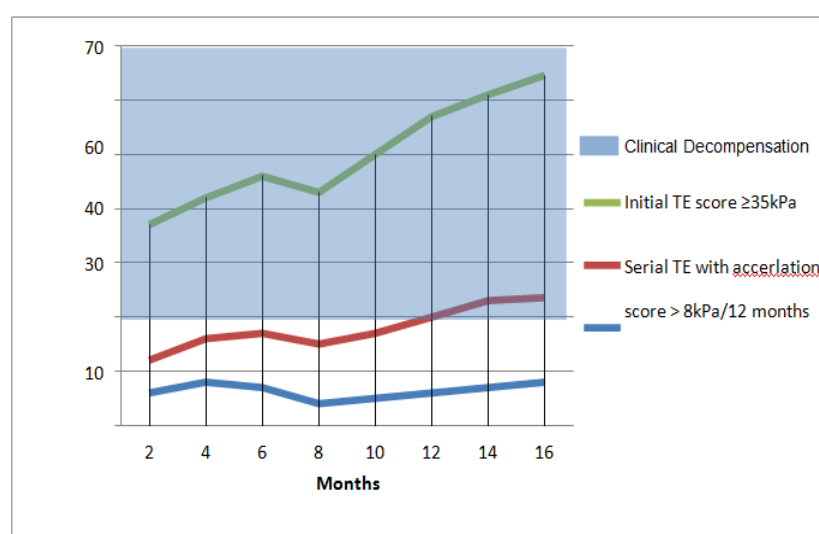


Figure 2B: Correlation between serial Transient Elastography (TE) measurements over time and clinical hepatic decompensation

Table1: patients demographic in cirrhosis and non-cirrhosis group

	Cirrhosis	Non cirrhosis
Gender (Male: Female)	(n=100) 65:35	(n=162) 111:51
Age (years)	53 ± 9.0	47.9 ± 10.5
Race (% White, Black/African America, Asian, mixed, and other)	84.4%, 3.9%, 9.1%, 0, 2.6%	87%, 4.2%,4.7%,1%, 3.2%
Ethnicity (Non-Hispanic vs Hispanic)	94% - 4%	98%-2%
BMI	31.7 ± 4.5	36.55 ± 4.3
Etiology of liver disease (%HCV,NASH,ALD,HBV,HCV/HIV,AIH,AIH-PBC)	72.2%,9.1%,10.4%,6.5%,1.3%,0,0	74.5%,7.3%,5.7%,5.7%,4.7%,1.6%,0.5%

clinical outcomes within the logistic regression analysis. A total of 143 patients had an increase in serial TE score an annual follow up. An Annual increase in TE score of ≥ 8 kPa in the cirrhotic range (≥ 12.5 kPa) was associated with a significant odds ratio (OR) 2.8 (95% CI 2.1-3.9, $p < 0.01$) for developing clinical decompensation and primary outcome (figure 2a, 2b).

Discussion

Clinical advances in medicine allowing early diagnosis of chronic liver disease by bringing an alternative to invasive procedures such as tissue liver biopsy with Fibroscan® or Transient elastography (TE) [14,18]. TE is a non-invasive, safe, and relatively cost-effective method providing immediate results not only by diagnosing cirrhosis but also by staging hepatic fibrosis and identifying different liver diseases pathologies. Many studies suggest low TE score of less than 10 kilopascals (KpA) rule out chronic liver disease patients [14,15]. While high TE scores of more than 12.5 kpa predicts advanced fibrosis. High TE score also predicts clinical decompensation and portal hypertension [19,30,28] Clinical signs of decompensation start appearing after an increase in portal venous pressure more than >15 mmHg after an increase in Hepatic Venous Gradient Pressure (HVGP) higher than 10-12 mmHg. Several studies suggest TE cut offs of 12.5 kPa as having a PPV of 77% and an NPV of 98% for excluding patients without advanced liver disease [22,23,26]. A large meta-analysis evaluating TE in chronic liver disease patients determined an optimal cut off for METAVIR stages F3-F4 and F4 as being 8.8 kPa and 11.7 kPa, respectively [24]. TE is a valuable tool in measuring portal venous pressure in comparison to other invasive procedure. These include the liver biopsy quantifying collagen deposition with bridging fibrosis on trichrome staining, invasive Hepatic Venous Measurements (HVPM), and upper endoscopy looking for signs of portal hypertension [35]. These facts are very reassuring for many patients with chronic liver disease to avoid unnecessary interventions. Hence, the current Baveno 6 consensus guidelines advising an annual TE measurement in combination with platelets count in patients with TE score < 20 kPa to safely avoid endoscopic evaluation [31]. Our cohort provides similar results, however, on a large-scale retrospective data over a long period of four and a half years. TE score of 12.5 kPa or higher associated with signs of portal hypertension.

Furthermore, our data showing cirrhosis patients with higher TE score of 20 kPa or higher exhibiting signs of progressive portal hypertension with stage II-IV of esophageal varices and severe Portal Hypertensive Gastropathy (PHG).

The utility of serial TE measurements has proven beneficial in prognosticating chronic liver disease patients and anticipate hepatic decompensation in compare to other non-invasive methods such as FIB-4 [16,17,25,27,28]. A large scale of data suggesting that TE predicts hepatic decompensation from a meta-analysis for a total of six studies pointing that TE with a score of more than 9-12.5 kpa increase the risk of hepatic decompensation with a RELATIVE RISK (RR) of 1.07 and a confidence interval (CI) 95%, risk for Hepatocellular Cancer (HCC) with a RR of 1.11 and a CI 95%; and risk of death from hepatic decompensation with a RR of 1.22 and a CI 95% [29]. Many other studies pointing toward the important role of TE in predicting clinical decompensation in cirrhosis [32,33,34,35]. 14% of our cohort developed clinical decompensation, mainly in cirrhosis (30%) with high TE score of higher than 12.5 Kpa. Historically, our cohort showed similar results with thirty patients with cirrhosis, TE score of >12.5 kpa TE score developing signs of clinical decompensation. Solely, cirrhosis patients with TE score of 35 kpa or higher considered a strong predictive indicator of clinical decompensation which included ascites, hepatic encephalopathy, variceal bleeding, an increase in Child's Pugh score >2 points, hepatocellular carcinoma, or death.

Strengths in this study that we were able to follow up patients over a long period of time which allows us to observe variable TE scores in patients experiencing hepatic decompensation. We are able to show through logistic regression analysis that an increase in TE score by 8 kPa over a 1 year period during the study had significantly higher odds of achieving a composite endpoint of clinical decompensation including ascites, hepatic encephalopathy, variceal bleeding, hepatocellular carcinoma, liver transplant, or death. These findings are novel and it has been supported by prior work using the Enhanced Liver Fibrosis (ELF) panel [36].

In conclusion, clinicians should screen cirrhosis patients with a high TE score of 12.5 kpa as this concludes cirrhosis with evidence of potential evidence of portal hypertension.

Careful attention for signs of clinical hepatic decompensations in cirrhosis patients with initial TE score of 35 kpa or higher AND those with 8 points increase in TE score over a 1 year period from the initial TE study.

Limitations in this study were the nature of study retrospective data analysis and limitations related to TE use in certain populations of chronic liver disease such as patients with decompensated cirrhosis with large volume ascites or prior major hepatic surgery causing scarring.

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