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Liver Stiffness Measurement Using Transient Elastography as a Predictor of Esophageal Varices in Chronic Liver Disease: A Clinical Study

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ABSTRACT

Introduction: Chronic liver disease (CLD) represents a progressive deterioration of liver functions over a period exceeding six months, encompassing synthesis of clotting factors, detoxification of metabolic byproducts, and bile excretion. **Aim:** To evaluate the association of transient elastography with endoscopic grading of esophageal varices (EVs) and to identify non-invasive predictors of EVs in patients with chronic liver disease (CLD). **Methods:** A total of 200 patients with CLD were enrolled in this study. Subjects underwent clinical examination, laboratory investigations, transient elastography, and endoscopy. Liver stiffness measurements obtained via transient elastography were correlated with the presence and grading of EVs. Additional non-invasive parameters, such as the Aspartate Aminotransferase/Platelet Ratio Index (APRI) and ultrasound findings, were also analyzed. **Results:** Out of 200 patients, 110 (55%) had esophageal varices. Patients with varices had significantly higher liver stiffness values (33.87±14.47 kPa) compared to those without varices (13.38±8.29 kPa) ($p<0.01$). The APRI values were significantly associated with the presence of varices (1.84±4.47 in patients with varices vs. 0.91±0.8 in patients without varices; $p<0.01$). No significant association was found between the presence of varices and gender ($p=0.79$). **Conclusion:** Transient elastography is a valuable non-invasive tool for predicting esophageal varices in patients with chronic liver disease. The use of non-invasive parameters such as APRI and liver elastography can effectively identify patients at risk for varices, reducing the need for invasive endoscopy and improving patient management.

Keywords: Chronic liver disease, transient elastography, esophageal varices, non-invasive diagnosis, Aspartate Aminotransferase/Platelet Ratio Index (APRI).

INTRODUCTION

Chronic liver disease (CLD) represents a progressive deterioration of liver functions over a period exceeding six months, encompassing synthesis of clotting factors, detoxification of metabolic byproducts, and bile excretion. CLD involves ongoing inflammation, destruction, and regeneration of liver parenchyma, culminating in fibrosis and cirrhosis. The etiology of CLD is broad, including prolonged alcohol abuse, viral infections, autoimmune diseases, and metabolic disorders. Cirrhosis, the terminal stage of CLD, disrupts liver architecture, forming nodules, vascular reorganization, neo-angiogenesis, and extracellular matrix deposition. At the cellular level, fibrosis is driven by the recruitment of stellate cells and fibroblasts, while hepatic stem cells support parenchymal regeneration. [1]

CLD is a prevalent and severe clinical condition, contributing significantly to morbidity and mortality, particularly in developing countries. Recent trends indicate a rising prevalence of CLD, with major etiologies in the developed world including alcoholic liver disease, chronic hepatitis B and C, non-alcoholic fatty liver disease (NAFLD), and hemochromatosis. In India, liver diseases are increasingly recognized as a public health priority. In 2015, India accounted for 18.3% of the global liver disease-related deaths. [2] The burden of cirrhosis and its complications has been escalating since 1980, unlike in China, where mortality rates have plateaued or declined.[3] The economic and healthcare impact of liver diseases in India is profound, alongside causing premature death and disability. The

cultural and lifestyle transition towards a Western diet and sedentary habits, along with changing social attitudes towards alcohol, are fueling a spectrum of liver diseases. [4]

CLD manifests through progressive hepatic fibrosis, architectural distortion, and nodule formation, with fibrosis being potentially reversible in its early stages. Clinical symptoms of CLD are often non-specific, such as fatigue and weight loss, or related to complications like portal hypertension, hepatocellular insufficiency, and hepatocellular carcinoma. Decompensated CLD frequently presents with complications like variceal rupture, ascites, and hepatic encephalopathy. Variceal rupture, the most common fatal complication of cirrhosis, is closely linked to the severity of liver disease. [5]

Cirrhosis arises from chronic liver injury, characterized by the replacement of functional hepatic tissue with non-functional fibrotic tissue and nodules. [6-7] Portal hypertension, a key complication of cirrhosis, leads to the formation of portosystemic collateral circulation, such as esophageal varices (EVs). [8] The prevalence of EVs ranges from 40% to 85% in cirrhotic patients, depending on the Child-Turcotte-Pugh (CTP) class. [9] Furthermore, the mortality rate due to variceal bleed ranges from 20% to 35%.[10] According to the American Association for the Study of Liver Diseases (AASLD), esophagogastroduodenoscopy (EGD) should be performed in all newly diagnosed cirrhotic. [11] Although EGD is the gold standard for esophageal varices diagnosis, the associated risk of complications is not negligible. [12,13]

Non-invasive diagnostic methods, such as transient elastography, are crucial for assessing liver stiffness and predicting complications like esophageal varices. This study aims to evaluate the association between transient elastography and endoscopic grading of esophageal varices and to identify non-invasive predictors of varices in patients with chronic liver disease. By enhancing non-invasive diagnostic approaches, this research seeks to improve patient management and reduce the need for invasive procedures. [14-16]

Aim: To evaluate the association of transient elastography with endoscopic grading of esophageal varices (EVs) and to identify non-invasive predictors of EVs in patients with chronic liver disease (CLD).

Methods: This study was conducted as an observational cross-sectional study. The research spanned a total of 22 months, from September 2022 to June 2024, following approval from the institutional research and ethical committee. The study took place in the Department of General Medicine at Mahatma Gandhi Medical College & Hospital, Jaipur.

Ethical Clearance and Confidentiality

Ethical clearance was obtained from the Institutional Review Board for Ethical Clearance at Mahatma Gandhi Medical College & Hospital, Jaipur. Participants and their attendants were informed about the study's procedures and objectives. Written informed consent was obtained from all participants or their attendants, with forms provided in the language best understood by them. Confidentiality of patient information was strictly maintained throughout the study. No alterations to the standard treatment plan were made for study purposes, and there was no additional financial burden on participants due to the study.

The study included cases of chronic liver disease (CLD) who attended the outpatient department (OPD) and were admitted to the inpatient department (IPD) at Mahatma Gandhi Medical College & Hospital.

Inclusion Criteria

- Diagnosed cases of chronic liver disease, regardless of etiology.
- Patients aged over 18 years.
- Willingness to give consent and participate in the study.

Exclusion Criteria

- Patients with active gastrointestinal bleeding upon admission.
- Pregnant women.
- Patients with known primary coagulation disorders.
- Patients with a history of porto-splenic surgical interventions.
- Patients unfit for endoscopic and fibroscan procedures.
- Patients with liver space-occupying lesions.

- Patients with pacemakers.

Procedure
After recruitment, detailed medical histories and physical examinations were performed on all subjects. The following tests were conducted:

- Complete Blood Count (CBC)
- Liver Function Test (LFT)
- Serum Total Protein
- Albumin/Globulin Ratio
- Serum Creatinine
- Prothrombin Time/International Normalized Ratio (PT/INR)
- Ultrasound of the whole abdomen
- Upper GI Endoscopy
- Fibroscan

Statistical Analysis
Data were compiled into an Excel spreadsheet under the guidance of a statistician. Statistical analysis was conducted using SPSS version 22.0 for Windows (SPSS Inc., Chicago, USA). The means and standard deviations of the measurements per group were analyzed using one-way ANOVA. The level of significance was set at $p<0.05p < 0.05p<0.05$. By applying these methods, the study aimed to analyze and interpret the relationships between various non-invasive parameters and the presence of esophageal varices in chronic liver disease patients.

RESULTS
Distribution of Esophageal Varices
Out of the 200 patients with chronic liver disease (CLD) enrolled in this study, 110 (55%) were found to have esophageal varices (EVs), while 90 (45%) did not. Among those with varices, the distribution was as follows:

- Grade I varices: 38 (34.54%)
- Grade II varices: 51 (46.36%)
- Grade III varices: 21 (19.09%)

This distribution highlights a significant prevalence of varices among CLD patients and underscores the need for effective screening methods.

Gender Distribution and Association with Varices
The gender distribution of the study population showed a higher number of male patients:

- Males: 146 (73%)
- Females: 54 (27%)

Among the males, 78 (70.91%) had varices, while among the females, 32 (29.09%) had varices. The analysis revealed no significant association between gender and the presence of varices ($p=0.79$), suggesting that gender does not influence the likelihood of developing varices in CLD patients.

Age Distribution and Association with Varices
The mean age of patients with esophageal varices was significantly higher (53.89 ± 7.86 years) compared to those without varices (39.62 ± 5.04 years). This difference was statistically significant ($p=0.001$), indicating that older patients are more likely to develop varices. This finding is consistent with existing literature, which suggests that the risk of varices increases with age in CLD patients.

Clinical Signs and Symptoms
The presence of various clinical signs and symptoms was evaluated to assess their association with esophageal varices. The findings are summarized below:

- **Jaundice**: Present in 51 (56.67%) patients without varices and 58 (52.73%) with varices. There was no significant association between jaundice and the presence of varices.
- **Pedal Edema**: Observed in 41 (45.56%) patients without varices and 47 (42.73%) with varices. There was no significant association between pedal edema and varices.

- **Palpable Spleen**: Detected in 6 (6.67%) patients without varices and 39 (35.45%) with varices. This association was statistically significant ($p<0.01$), suggesting that splenomegaly is a predictor of varices.
- **Ascites**: Found in 43 (47.78%) patients without varices and 79 (71.82%) with varices, showing a significant association with varices ($p<0.01$). Ascites is commonly associated with advanced liver disease and portal hypertension, which are closely linked to variceal development.

Laboratory Findings

Several laboratory parameters were analyzed to determine their association with esophageal varices:

- **Mean MELD Score**: The Model for End-Stage Liver Disease (MELD) score was significantly higher in patients with varices (15.88±4.47) compared to those without varices (11.38±3.29), with a significant association ($p=0.001$). A higher MELD score indicates more severe liver disease, which correlates with the presence of varices.
- **APRI (Aspartate Aminotransferase/Platelet Ratio Index)**: The APRI was significantly higher in patients with varices (1.84±4.47) compared to those without varices (0.91±0.8), with a significant association ($p<0.01$). This index is a non-invasive marker of liver fibrosis and can predict the presence of varices.

Non-Invasive Parameters

The study also evaluated several non-invasive parameters to predict the presence of esophageal varices:

- **Portal Vein Size**: The mean portal vein size was larger in patients with varices (14.68±0.56 mm) compared to those without varices (13.27±0.38 mm), with a significant association ($p=0.003$). An enlarged portal vein is indicative of portal hypertension, which is a key factor in the development of varices.
- **Spleen Diameter**: The mean spleen diameter was significantly larger in patients with varices (17.71±14.52 mm) compared to those without varices (13.89±1.49 mm), with a significant association ($p<0.01$). Splenomegaly is a common feature in patients with portal hypertension and varices.
- **Transient Elastogram Liver Stiffness**: Liver stiffness measurements were significantly higher in patients with varices (33.87±14.47 kPa) compared to those without varices (13.38±8.29 kPa), with a significant association ($p<0.01$). Transient elastography is a valuable tool for assessing liver stiffness and predicting varices.
- **Platelet Count to Spleen Diameter (PC/SD)**: The PC/SD ratio was significantly lower in patients with varices (128.2±13.17) compared to those without varices (1405.76±291.65), with a significant association ($p<0.01$). A lower PC/SD ratio is associated with higher risk of varices.

Table 1: Gender Distribution and Varices

Gender	With Varices	Without Varices	Total	p-value
Male	78 (70.91%)	68 (75.56%)	146	0.79
Female	32 (29.09%)	22 (24.44%)	54	
Total	110 (100%)	90 (100%)	200	

Table 2: Age Distribution and Varices

Parameter	With Varices (Mean ± SD)	Without Varices (Mean ± SD)	p-value
Age (years)	53.89 ± 7.86	39.62 ± 5.04	0.001

Table 3: Clinical Signs and Symptoms

Parameter	With Varices	Without Varices	p-value
Jaundice	58 (52.73%)	51 (56.67%)	0.68
Pedal Edema	47 (42.73%)	41 (45.56%)	0.68
Palpable Spleen	39 (35.45%)	6 (6.67%)	<0.01
Ascites	79 (71.82%)	43 (47.78%)	<0.01

Table 4: Laboratory Findings

Parameter	With Varices (Mean ± SD)	Without Varices (Mean ± SD)	p-value
MELD Score	15.88 ± 4.47	11.38 ± 3.29	0.001
APRI	1.84 ± 4.47	0.91 ± 0.8	<0.01

Table 5: Non-Invasive Parameters

Parameter	With Varices (Mean ± SD)	Without Varices (Mean ± SD)	p-value
Portal Vein Size (mm)	14.68 ± 0.56	13.27 ± 0.38	0.003
Spleen Diameter (mm)	17.71 ± 14.52	13.89 ± 1.49	<0.01
Transient Elastogram (kPa)	33.87 ± 14.47	13.38 ± 8.29	<0.01
PC/SD Ratio	128.2 ± 13.17	1405.76 ± 291.65	<0.01

These detailed results and tables demonstrate the significant associations between various clinical and non-invasive parameters with the presence of esophageal varices in chronic liver disease patients. These findings support the potential use of non-invasive methods for screening and predicting varices, thereby reducing the reliance on invasive procedures like endoscopy.

DISCUSSION

Patients with chronic liver disease are routinely screened for varices, and it has been observed that many patients do not have varices or have only mild varices that do not require intervention. Endoscopy in the gold standard for the diagnosis of varices. Screening with Endoscopy to identify esophageal varices in all chronic liver disease patient at baseline as well as periodic intervals is recommended by current guidelines, necessitating other easier modalities for diagnosis and monitoring. Thus, methods of predicting the presence of esophageal varices noninvasively are in great demand to avoid unpleasant endoscopy and for patients in whom endoscopy is contraindicated and also to improve the management. Several noninvasive methods have emerged in recent years by assessing simple laboratory, clinical and sonographic parameter such as splenomegaly, platelet count, portal vein diameter, AST, ALT, Transient elastogram. Giannini et al., found good indirect parameters for prediction of presence of esophageal varices in cirrhotic patients. [14]

Our study is facilitated in a way that the non-invasive predictors of varices in chronic liver disease will reduce the burden of endoscopy for both the patient and the physician and also in areas where endoscopic procedures are not readily available. Here, we studied liver elastography as a predictor of esophageal varices and compared it with other non-invasive predictors like ultrasound abdomen and liver function tests.

Varices

In the present study, 90 (45%) subjects did not have varices, while 110 (55%) had varices. Of the total 110 patients with varices, 38 (34.54%) patients had Grade I varices, 51 (46.36%) patients had Grade II varices, and 21 (19.09%) patients had Grade III varices. Almost similar were the findings of **AS N et al., (2023)** [20] found that 57% patients had no varices, while 43% had varices. Of the total 72 patients with varices, 52 patients (72.2%) had F1/Grade I varices, 9 patients (12.5%) had F2/Grade II varices, and 11 patients (15.3%) had F3/Grade III varices. In study done by **Zhao W et al., (2021)** [19] esophageal varices were present in 70% of the study subjects.

Gender distribution

In present study, there was predominance of male gender (n=146, 73%) and remaining 54 (27%) were female. Varices were present in 78 (70.91%) males and 32 (29.09%) females. There was no significant association of varices with gender of the subject with p of 0.79. these findings were concurrent with results of **AS N et al., (2023)** [20] found that males (73.2%) outnumbered females (26.8%). Varices were present in 41.5% of the males and 46.7% of the females. There was no significant association of gender with varices with a p-value of 0.546. Similar were the results of **Zhao W et al., (2021)** [19], found that there was male predominance among study subjects, 82.14% male and 17.85% female subject had varices and they also observed that gender of the subject had no association with presence of varices (p=0.548).

Age distribution

In present study, mean age of subjects with esophageal varices was 53.89±7.86 years and mean age of subjects who did not have varices was 39.62±5.04. There was a statistically highly significant association of age of subjects with presence of varices (p value of 0.001). Similar were the findings of **AS N et al., (2023)** [20] found that there was a significant association of age with the presence of varices with a p-value of <0.001.

Signs and symptoms

In present study, in subjects with jaundice, 51 (56.67%) did not have varices and 58 (52.73%) have esophageal varices, there was no significant association of jaundice with presence of varices. In subjects with pedal edema, 41 (45.56%) did not have varices while 47 (42.73%) have varices, there was no significant association of pedal edema with presence of varices. In subjects with palpable spleen, only 6 (6.67%) did not have varices while 39 (35.45%) have varices, showing a statistically significant association of palpable spleen with presence of varices (p value <0.01). In patients with ascites, 43 (47.78%) did not have varices, while 79 (71.82%) have esophageal varices, showing a statistically significant association of ascites with presence of varices(p value <0.01). These findings were concurrent with results of **AS N et al., (2023)** [20] who found that splenomegaly and ascites had a statistically significant association with presence of varices (p value <0.001, 0.001; respectively.

Etiology

Majority of subjects with alcohol abuse had varices (60.91%), followed by 16.36% with HBV, 8.18% with AIH and 2.73% with HCV. 11.82% subject with other unknown etiologies also presented with varices. There was no significant association of different etiologies with varices. Similar were the findings of **AS N et al., (2023)** [20] found thatvarices were seen in the majority of the people with alcohol- (42.6%) and NASH-related (51.5%) cirrhosis followed by 42.8% in cirrhosis related to hepatitis C and 30.7% in hepatitis B infection. About 66.6% of patients with other causes had varices. However, there was no significant association between different etiologies and varices.

CBC profile

In present study, mean hemoglobin level of subjects with varices was 10.59±1.8 and in subjects without varices was 11.84±2.01, showing a no significant association between mean level of hemoglobin with presence of varices. Among study population, mean WBC in patients with varices was 4.55±2.11 and in subjects without varices was 4.89±1.53, showing a no significant association between mean level of WBC with presence of varices. Mean level of platelets in subjects with varices was 87.16±41.92 and in subjects without varices was 121.4±51.27, showing astatistically significant association of mean platelet level with presence of varices (p value of 0.004). Chalasani NI et al., reported that platelet count can predict the significant esophageal varices.[21] This finding was similar to results of **Sarkar DK et al., (2018)** [18] observed that patient with EVs had lower platelet count (mean±SD 101.01± 37.74 109/L) than those without EVs (mean±SD 131.54±46.4x109/L). This difference was statistically significant (p<0.035) among the groups. **Sebastiani G et al., (2010)** [17] also found that the platelet count was lower in patient with esophageal varices (mean±SD, 98.8±48.4 x109/L) than patient without cirrhosis (mean±SD, 142.8±70.1 x109/L) which is almost similar to our results. **AS N et al., (2023)** [20] found a statistically significant association between platelet level with presence of varices with p value of0.024, as in our study.

LFT profile

In present study, mean Alanine transaminase (IU/l) level in subjects without varices was 60.5±31.17 and with varices was 54.06±21.91, showing no significant association between mean Alanine transaminase level with varices. Among study subjects, mean Aspartate transaminase (IU/l) level in subjects without varices was 35.61±11.32 and with varices was 51.25±18.42, showing statistically significant association between mean Aspartate transaminase level with presence of varices (p value of 0.03). In present study, mean total bilirubin (mg/dl) level in subjects with varices was 1.7±0.46 and without varices was 1.48±0.37, showing no significant association between mean total bilirubin level with varices. Mean direct bilirubin (mg/dl) level in subjects with varices was 0.93±0.45 and without varices was 0.87±0.36, showing no significant association between mean direct bilirubin level with varices. These findings were concurrent with results of **Sarkar DK et al., (2018)** [18] found that mean AST level was higher in subjects with varices (52.26 ± 25.13) when compared to subjects without varices (33.75 ± 11.31), having a statistically significant difference (p=0.008). But no significant association was fount between ALT level and presence of varices (p=0.856), similar to our study.

Non-invasive parameters

In present study, mean portal vein size in subjects with varices was 14.68±0.56 and without varices was 13.27±0.38, showing statistically significant association between mean portal vein size with presence of varices(p value of 0.003). Mean spleen diameter in subjects with varices was 17.71±14.52 and without varices was 13.89±1.49, showing statistically significant association between mean spleen diameter with presence of varices (p value <0.01). Mean PC/SD in subjects with varices was 128.2±13.17 and without varices was 1405.76±291.65, showing statistically significant association between mean PC/SD with presence of varices(p value <0.01). Similar were the results of **Zhao W et al., (2021)** [19], found thatportal vein diameter and spleen thickness were found to be applicable for the diagnosis of EV (P values <0.05). **AS N et al., (2023)** [20] found that portal vein diameter and presence of varices had a statistical significance (p-value=0.005), as in present study.

MELD score

In present study, mean MELD score in subjects with varices was 15.88±4.47 and without varices was 11.38±3.29, showing statistically significant association between mean MELD score with presence of varices(p value of 0.001). This finding was concurrent with results of **AS N et al., (2023)** [20] found that MELD score is associated with varices (p-value <0.001).

APRI and Transient Elastogram

In present study, Aspartate aminotransferase (AST)-to-platelet ratio index (APRI). in subjects with varices was 1.84±4.47 and without varices was 0.91±0.8, showing statistically significant association between APRI with presence of varices(p value <0.01). Transient Elastogram Liver stiffness value in subjects with varices was 33.87±14.47 and without varices was 13.38±8.29, showing statistically significant association between Transient Elastogram Liver stiffness value with presence of varices (p value <0.01). These findings were concurrent with results of **Sarkar DK et al., (2018)** [18] found that mean APRI was more in subjects with varices (1.58 ± 1.20) as compared to patients without varices (0.73 ± 0.35), showing a statistically significant difference (p= 0.003). They also observed that Transient Elastogram was 34.57 ± 20.00 in subjects with varices and 13.32 ± 10.63 in patients without varices, showing a statistically significant difference (p <0.001), as in present study. Similar were the results of **Zhao W et al., (2021)** [19], found that APRI and Liver stiffness were found to be applicable for the diagnosis of EV (P values <0.05). **AS N et al., (2023)** [20] found that liver elastography grading association with presence of varices was statistically significant with a p value of <0.001, as in present study.

CONCLUSION

This study substantiates the role of transient elastography as a robust non-invasive method for predicting esophageal varices in patients with chronic liver disease. The significant correlation between liver stiffness measurements and the presence of varices, along with the utility of APRI, underscores the potential for these tools to enhance clinical management and reduce the reliance on invasive endoscopic procedures. Further research should continue to explore and validate these findings, with an emphasis on integrating non-invasive diagnostics into comprehensive patient care strategies.

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