# Role of Transient Elastography in Early Detection of HCC in Cirrhotic Patients

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**Background and study aim:** Hepatocellular carcinoma (HCC) is common primary malignancy of the liver and one of the most frequent causes of death in patients with liver cirrhosis**.** Nowadays, liver stiffness measured non-invasively by transient elastography has been reported to be well correlated with histologically assessed liver fibrosis stage**.** The degree of liver fibrosis is the strongest indicator of risk for HCC development, that's why liver stiffness measured by transient elastography is helpful in demarcating patients at a high risk for HCC, who need frequent check-up by imaging examinations.The aim of this study was to study the role of ultrasound elastography (FibroScan) in early detection of hepatocellular carcinoma in cirrhotic patients as well as verifying whether ultrasound elastography (Fibro-Scan), could be used as a tool for identifying cirrhotic patients who are at high risk of developing HCC.

**Patients and Methods:** This study included 100 patients; 50 with HCC and 50 cirrhotics without evidence of HCC . For all groups, clinical data and image findings were studied. Tumour characteristics were assessed including size, number and site. Tumor staging was done using Okuda, CLIP, VISUM and Tokyo staging systems. Transient elastography was done for all patients and the results were expressed in kilopascal.

**Results:** Liver stiffness was significantly higher in HCC patients compared to cirrhotic patients. The sensitivity and specificity in diagnosis of HCC were 72% and 84% respectively at cut-off of 30.4 kpa with 91.1% accuracy. Fibroscan has a positive significant correlation with tumour size (P<0.001), Child–Pugh (P<0.001), Okuda classification (P<0.001), CLIP staging (P<0.001) and Tokyo classification (P<0.001) among HCC patients. It was found that likelihood of HCC risk was correlated with increase of liver stiffness. At liver stiffness of 25-30 kpa the probability of HCC is 91% so, these patients should undergo close follow up. Patients with stiffness ≥30 kpa had HCC.

**Conclusion:** Fibroscan could be used for early detection of HCC in cirrhotic patients and determining the patients who are at high risk for developing HCC.

## INTRODUCTION

Hepatocellular carcinoma is common primary malignancy of the liver and one of the most frequent cause of death in patients with liver cirrhosis **[1]**. It is one of the most challenging tumors with high incidence, prevalence and mortality rates in Egypt **[2]**. Nowadays, liver stiffness measured noninvasively by transient elastography has been reported to be well correlated with histologically assessed liver fibrosis stage **[3]**. The degree of liver fibrosis is the strongest indicator of risk for HCC development, that's why liver stiffness measured by transient elastography is helpful in demarcating patients at a high risk for HCC, who need frequent check-up by imaging examinations **[4]**. This work aimed to study the role of ultrasound elastography (FibroScan) in Early Detection of Hepatocellular Carcinoma in Cirrhotic Patients as well as verifying whether ultrasound elastography (FibroScan), could be used as a tool for identifying cirrhotic patients who are at high risk of developing HCC.

## PATIENTS AND METHODS

This study was approved by the ethics and research committee of Benha faculty of medicine, Benha University, Egypt. and all patients included in this study had the procedure thoroughly explained to them. All patients included in this study had the procedure thoroughly explained to them.

This study was conducted on 100 patients with cirrhosis of both sexes who were attending Shebin Elkom Fever Hospital, Menofyia Governorate in the period from October 2014 to November 2015.

**The studied patients were classified into :**
Group I which included 50 patients with Cirrhosis and HCC diagnosed by ultrasound examination and confirmed by triphasic computed tomography. And Group II which included 50 patients with Cirrhosis and without evidence of HCC diagnosed by clinical, laboratory and ultrasound examination **[5]**.

Patients with cirrhosis and Patients with HCC within Milan Criteria were included in this study. While patients with morbid obesity, ascites, hepatic metastatic lesions and patients with HCC beyond Milan criteria were excluded from this study.

HCC was diagnosed by abdominal US and confirmed by triphasic CT scan. AFP was assayed by an enzyme immunoassay (EIA) Kit (Roche Mannheim, Germany). The clinical/pathological data of the patients were recorded, including age, sex, viral infections [Hepatitis C Virus (HCV) and Hepatitis B Virus (HBV)], alcohol intakes, biochemical liver function test results, and AFP levels. Severity of liver disease was assessed by modified Child-Pugh score **[17]** and MELD (model for end stage liver disease) score [18] and the updated MELD (uMELD) score **[19]**. Tumor characteristics were detected by abdominal US with or without CT scan (including tumor size, number, site, halo sign and neovascularization). Tumor staging was done using Okuda **[6]**, The Cancer of the Liver Italian Program (CLIP) **[7]**, VISUM (Vienna survival model for HCC) **[8]**, Tokyo **[9]** staging systems and Barcelona Clinical Liver Cancer Staging (BCLC Staging System) **[10]**.

**Blood sampling and biochemical assays**
Fasting venous blood samples (5 ml) were collected by trained laboratory technicians. A portion of blood was allowed to clot and then centrifuged at 3500g for 5 min to separate the serum used for assessment of aspartate amino-transferase (AST), alanine aminotransferase (ALT), total bilirubin, direct bilirubin, albumin, creatinine and glucose concentrations were assayed using Beckman CX4 chemistry analyzer (NY, USA, supplied by the Eastern Co. For Eng. & Trade-Giza, Egypt). Viral infection status (HCV Ab and HBsAg) were measured using Abbott, Axyam (USA, Supplied by Al kamal company). Serum AFP level was determined using an enzyme-linked binding protein assay kit. All assays were performed in duplicate according to the manufacturer's instructions.

**Specific examination**
Liver stiffness was measured for patients using the transient elastogrpahy machine "Fibroscan" manufactured by Echosens. Results were expressed in kilo Pascals (kPa) and 10 validated measurements were recorded for each patient.

**Statistical analysis**
The statistical analysis was conducted using STATA/SE version 11.2 for Windows (STATA corporation, College Station, Texas).

The collected data were summarized in terms of mean± Standard Deviation (SD) and range for quantitative data and frequency and percentage for qualitative data. Comparisons between the different study groups were carried out using the Chi-square test ($\chi 2$) and Fisher Exact test (FET) to compare proportions as appropriate. The Student t-test (t) was used to detect difference in the mean between two parametric data, while the Mann-Whitney test (z) was used to compare two non-parametric data. Receiver Operating Characteristics (ROC) analysis was carried out to evaluate the diagnostic performance of stiffness for HCC screening among cirrhotic patients. The best cutoff point and the corresponding sensitivity and specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV) and Area under the Curve (AUC) were estimated. Likelihood of presence of HCC is conducted using Stratum Specific Likelihood Ratio (SSLR). The significance level was set at $P<0.05$. A P value <0.001 was considered highly significant (HS) while a P value >0.05 was considered non-significant. The Pearson and Spearman correlation coefficient was used to test for the correlation between stiffness and different variables.

## RESULTS

The demographic features and characteristics of the (two patients' groups) were summarized in Table (1). A total of 100 adults, which included

50 patients with HCC and 50 patients with liver cirrhosis and without evidence of HCC.

In the current study, patients with HCC had a mean age of 53.5 years with a range between 44-68 years old, while cirrhotic non-HCC patients are younger with a mean age of 51.3 years and ranging between 39-67 years old. Also HCC commonly presented in males (84%) more than females (16%). 58% of HCC cases were from urban areas. Most of HCC cases were farmers (76%) while (24%) only were non-farmers. HCC was common in smokers than non-smokers. Regarding HCC etiology, the results showed that the frequency of HBV positivity had no statistically significant difference between the studied patients. It was not detected in HCC or Non-HCC cases HCV was present all cases with no statistically significant difference between the two groups. The liver functions in cirrhosis assessed by Child–Pugh classification among the studied patients showed that 16% of HCC cases were Child A, while 20% of HCC cases were Child B and 64% were Child C with no statistical significant difference between the two groups. There was no statistically significant difference among the two groups as regards the severity of liver disease assessed by MELD scores (Table 1).

Tumor imaging characteristics of HCC patients were illustrated in (Table 2). Abdominal CT showed that Cirrhosis was present in 100% of cases with HCC, most of cases had splenomegaly (94%). PVT was found in 14% of patients. Focal lesions by CT tended to be single, more in Right lobe, ≥3cm in diameter. Only 10% of patients had enlarged lymph nodes. As regard Okuda staging, most of HCC cases were in the late stage; stage III (46%), followed by stage II (38%) then stage I (16%). Concerning CLIP staging, most of HCC cases were presented at the intermediate stage II (62%) comparing to the patients presented at the early stage (10%) and the advanced stage (28%) respectively. According VISUM staging most of HCC cases (68%) were stage I. According to Tokyo staging, most of HCC patients were presented at advanced stage (58%) comparing to the patients presented at early stage (42%). As regards AFP levels, the data showed that AFP values were significantly different between HCC cases and cirrhotics (p=0.001).

In this study, liver stiffness was assessed using transient elastography (TE) and the measurements were expressed in Kilopascal. Liver stiffness and Inter Quartile Range measured by Fibroscan were significantly higher in HCC group (P=0.001). But, there was no statistical significant difference between the groups as regards the success rate (P= 0.052). (Table 3) and Figure (1).

In the receiver operating curve (ROC) (Table 4), Figure (2), the area under curve (AUC) was 91.18% when we use 30.4 kpa as a cut off point with sensitivity of 72%, specificity of 84%, positive predictive value of 81.82% and Negative predictive value of 75 %.

It was found that likelihood of HCC risk was correlated with increase of liver stiffness. At liver stiffness of <25 kpa, the probability of HCC presence was about 72% ,while stiffness of 25-30 kpa has a probability of 91% so, these patients should undergo close follow up. Patients with stiffness ≥30 kpa had HCC. There was significant positive correlation between liver stiffness by fibroscan and tumour size (P<0.001), Child–Pugh (P<0.001), Okuda classification (P<0.001), CLIP staging (P<0.001) and Tokyo classification (P<0.001) among HCC patients. Figures (3,4,5, 6,7) respectively.

**Table (1) :** Demographic features of the studied patients

| | HCC (N= 50) | | Non HCC (N= 50) | | P-value |
|---|---|---|---|---|---|
| **Age (years)**<br>Mean ± SD<br>Range | 53.5 ± 6.3<br>44 – 68 | | 51.3 ± 8.4<br>39 – 67 | | 0.14 |
| | **N** | **%** | **N** | **%** | |
| **Gender**<br>Male<br>Female | 42<br>8 | 84<br>16 | 38<br>12 | 76<br>24 | 0.31 |
| **Residence**<br>Rural<br>Urban | 21<br>29 | 42<br>58 | 36<br>14 | 72<br>28 | 0.42 |
| **Occupation**<br>Farmer<br>Non-farmer | 38<br>12 | 76<br>24 | 34<br>16 | 68<br>32 | 0.41 |
| **Smoking**<br>Yes<br>No | 28<br>22 | 56<br>44 | 34<br>16 | 68<br>32 | 0.21 |
| **HCV Ab** | 50 | 100 | 50 | 100 | |
| **HBs Ag** | 00 | 00 | 00 | 00 | |
| Severity of liver disease Child-Pugh Classification | | | | | |
| **Child A** | 8 | 16 | 11 | 22 | 0.59 |
| **Child B** | 10 | 20 | 22 | 44 | 0.49 |
| **Child C** | 32 | 64 | 17 | 34 | 0.52 |
| MELD Score | | | | | |
| **Range** | 7-45 | | 6-44 | | 0.79 |
| **Mean±SD** | 20.6±9.4 | | 19.9±9.1 | | |
| uMELD Score | | | | | |
| **Range** | 2-6.6 | | 2.6-7.1 | | 0.58 |
| **Mean±SD** | 4.2±1.18 | | 4.08±1.1 | | |

SD: standard deviation; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; HBs Ag: Hepatitis B surface Antigen.

**Table (2):** Tumor related findings and characteristics of HCC in the studied patients

| | HCC group N=50 | |
|---|---|---|
| | **N** | **%** |
| **Cirrhosis** | 50 | 100 |
| **Splenomegaly** | 47 | 94 |
| **Portal vein thrombosis** | 7 | 14 |
| **Number**<br>Single / 2 / multiple | 26 / 8 / 16 | 52 / 16 / 32 |
| **Site**<br>Rt lobe/ Lt lobe/both | 27/5/18 | 54 /10 /36 |
| **Size**<br><3cm / ≥3cm | 18 / 32 | 36 / 64 |
| **Lymph node** | 5 | 10 |
| **Tumor staging** | | |
| **Okuda staging** | | |
| **I / II / III** | 8 / 19 / 23 | 16 / 38 / 46 |
| **CLIP staging** | | |
| **I / II / III** | 5 / 31 / 14 | 10 / 62 / 28 |
| **VISUM staging** | | |
| **I / II / III** | 29 / 8 / 13 | 58 / 16 / 26 |
| **Tokyo staging** | | |
| Early (<5) / Advanced (≥5) | 21 / 29 | 42 / 58 |
| **AFP (ng/mL) level** | | |
| Range | 12.8-5300 | |
| Mean ± SD | 627.6± 1286 | |

AFP: Alphafetoprotein; CLIP: Cancer of the liver Italian program; HCC: hepatocellular carcinoma; VISUM: Vienna survival model.

**Table (3) :** Fibroscan results of the studied patients

| | HCC N=50 | | Non HCC N=50 | | P |
|---|---|---|---|---|---|
| | **Range** | **Mean ± SD** | **Range** | **Mean ± SD** | |
| **1-Stiffness** | 24.2-55 | 39.8±5.8 | 17.6-39.2 | 27.5±6.1 | **<0.001*** |
| **2-IQR** | 10-29 | 20.58±6.3 | 3-23 | 13.76±4.4 | **<0.001*** |
| **3- Success rate** | 87-100 | 98.4±4 | 76-100 | 94.8±8.8 | 0.052 |

* = significant
IQR = Inter Quartile Range

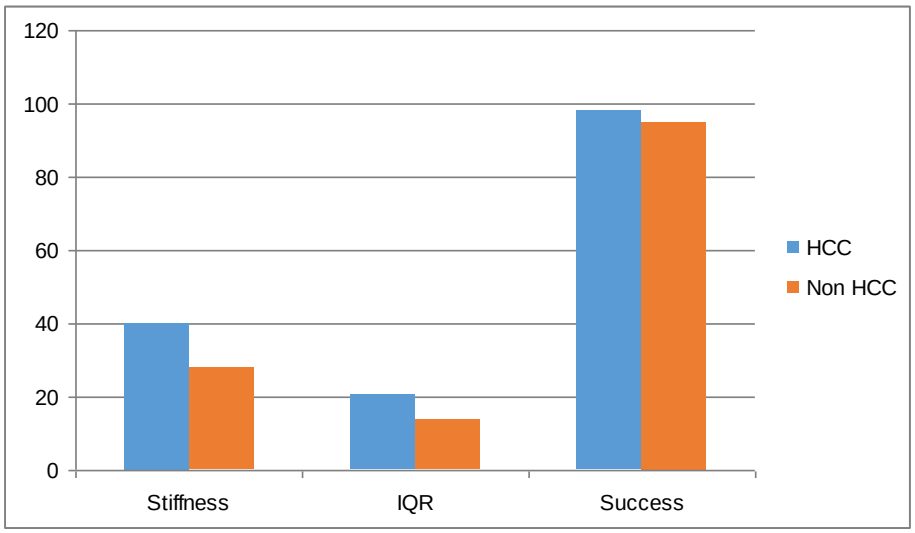


**Figure (1) :** Fibroscan results of the studied patients

**Table (4) :** ROC curve analysis of Stiffness in prediction of hepatocellular carcinoma

| | |
|---|---|
| Cutoff point | 30.4 kpa |
| Sensitivity (%) | 72.0% |
| Specificity (%) | 84.0% |
| PPV (%) | 81.82% |
| NPV (%) | 75.0% |
| AUC | 0.9118 |
| Correctly classified | 78.0% |

PPV=Positive predictive value
NPV=Negative predictive value
AUC = Area Under the Curve

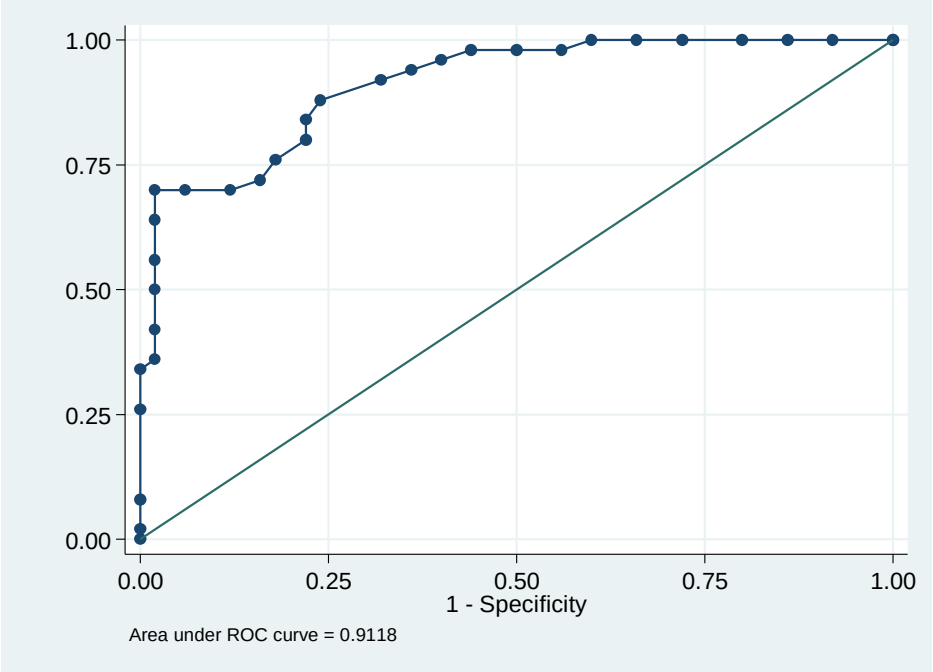


**Figure (2) :** ROC curve analysis of Stiffness in prediction of hepatocellular carcinoma

**Table (5) :** Stratum Specific Likelihood Ratio (SSLR) for HCC risk by measurement of liver stiffness

| Strata | Non HCC (No.=50) | | HCC (No.=50) | | SSLR |
|---|---|---|---|---|---|
| | No. | % | No. | % | |
| <25 | 11 | 22.0 | 8 | 16.0 | 0.7272 |
| 25-30 | 12 | 24.0 | 11 | 22.0 | 0.9167 |
| 31-35 | 7 | 14.0 | 7 | 14.0 | 1.00 |
| 36-40 | 14 | 28.0 | 16 | 32.0 | 1.1428 |
| >40 | 6 | 12.0 | 8 | 16.0 | 1.3333 |

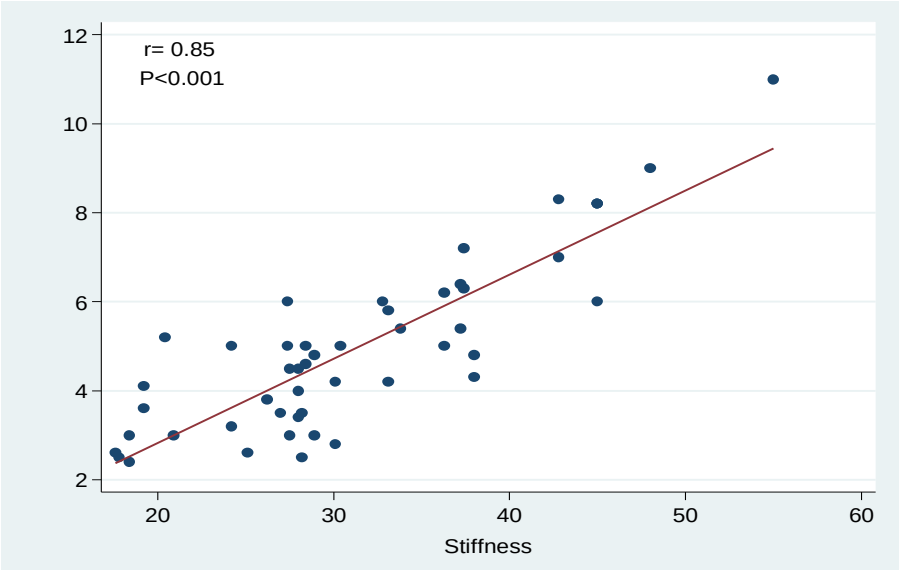


**Figure (3) :** Correlation between the size of the tumor and liver stiffness

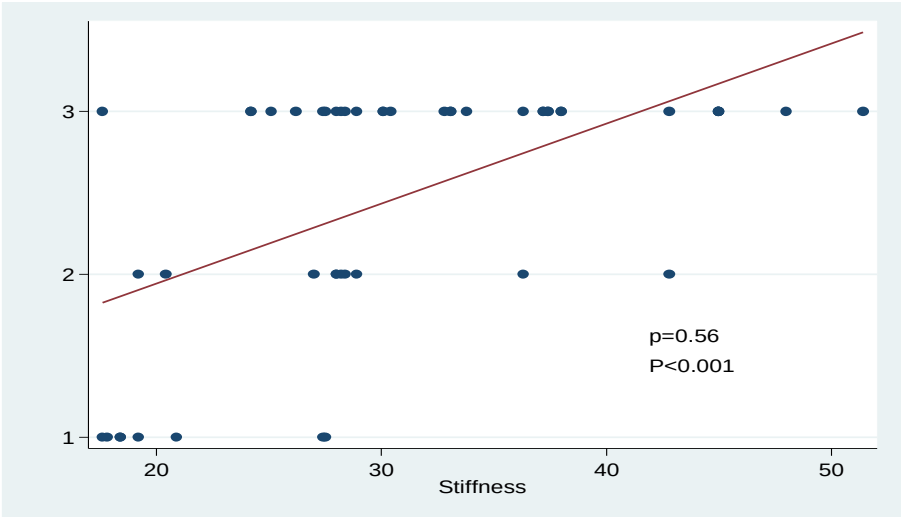


**Figure (4) :** Correlation between Child score and liver stiffness

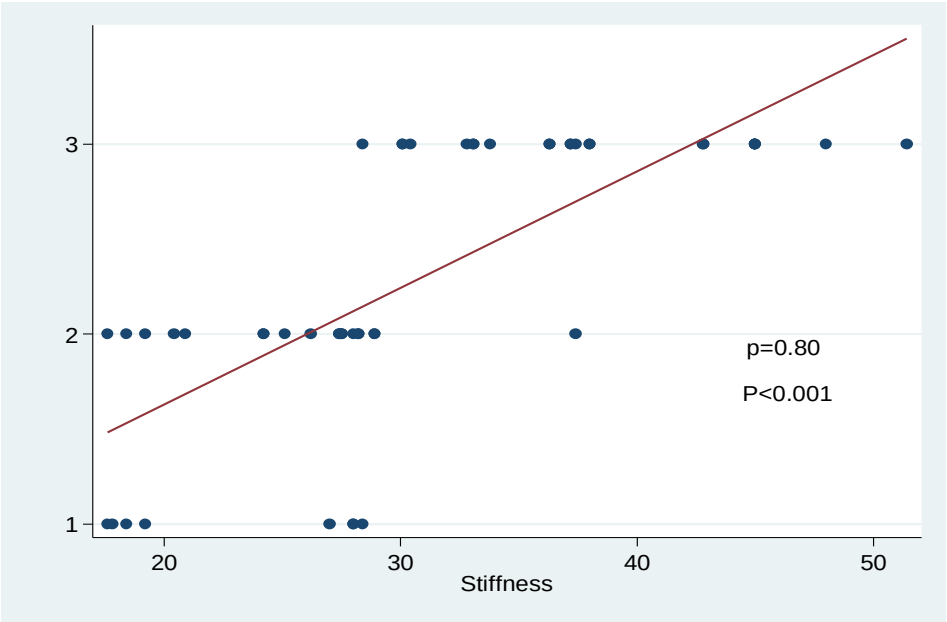


**Figure (5) :** Correlation between Okuda classification and liver stiffness

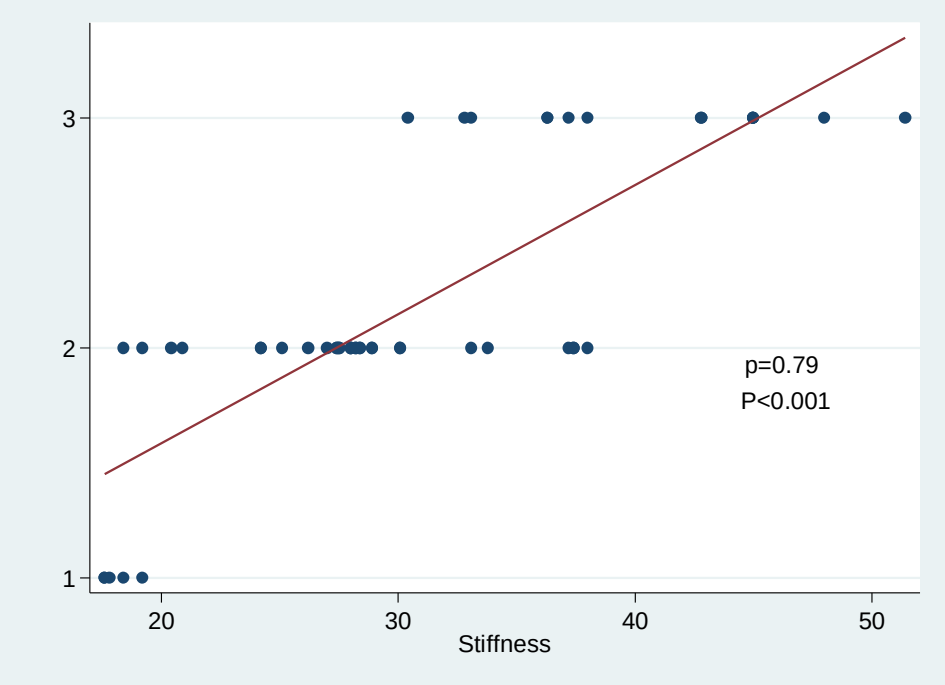


**Figure (6) :** Correlation between CLIP staging and liver stiffness

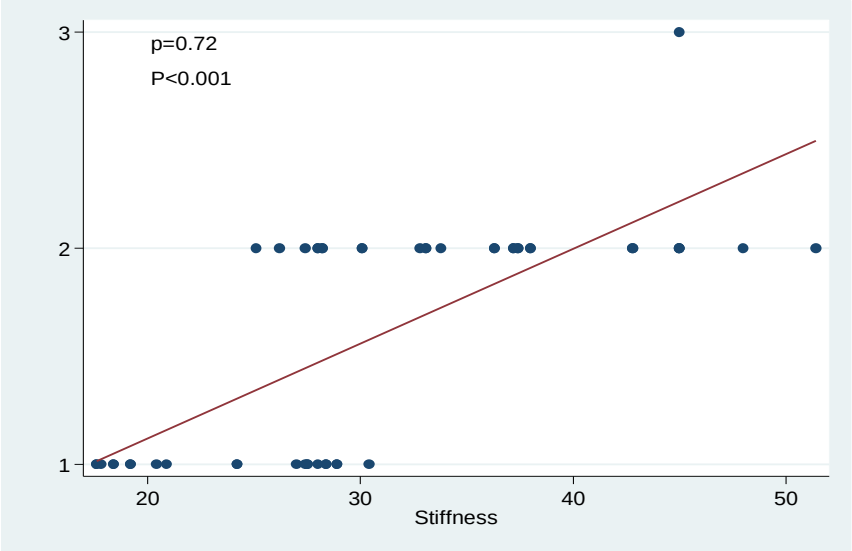


**Figure (7) :** Correlation between Tokyo classification and liver stiffness

## DISCUSSION

In this study, liver stiffness and Inter Quartile Range (IQR) measured by Fibroscan were significantly higher in HCC group. This goes in agreement with Mi Sung et al. **[11]** who stated that the presence of HCC is associated with higher values of fibroscan. In this study, when using ROC curve of fibroscan as a marker of HCC diagnosis, the cutoff value for HCC was 30.4 kpa with sensitivity of 72%, specificity of 84%, positive predictive value of 81.82% and negative predictive value of 75%. This was near the results of Foucher et al. **[12]**, who stated that the cutoff values for HCC which was 53.7kPa.

Also in this study, there was a significant positive correlation between the liver stiffness and the presence of HCC. Also, prediction of occurrence of HCC by fibroscan may be of useful value. SSLR for HCC presence by liver stiffness was 0.7272 in <25 kPa, 0.9167 in 25.1 to 30kPa, 1.00 in 30.1 to 35 kPa, 1.1428 in 35.1 to 40 kPa and 1.3333 in >40 kpa. These results were in agreement with Masuzaki et al. **[4]** and Yosry et al. **[13]** who stated that there is association between LSM and the risk of HCC development in chronic HCV patients. SSLR for HCC presence by liver stiffness was 0.0128 in <10 kPa, 0.8189 in 10.1 to 15 kPa, 4.285 in 15.1 to 25 kPa, and 15 in >25 kPa. This study showed that there was a significant positive correlation between results of fibroscan and Child-Paugh classification. It was found that fibroscan stiffness was higher in patients with Child B&C than patients with Child A classification.

This correlation was not discussed by researchers however, Pesce et al. **[14]** stated that patients with Child B&C had the highest value measured by fibroscan. Also, it was found that there was no correlation between MELD and uMELD Score and the stiffness measured by fibroscan. These results were different than those noted by Pesce et al. **[14]** who found that there was positive correlation between MELD and uMELD score and fibroscan results. They found that MELD score results more than 10 had stiffness about 29.07 Kpa while MELD score less than 10 had stiffness about 22.91 Kpa.

In this study, it was found that there was no correlation between tumour number and stiffness measured by fibroscan which is not discussed by researchers till now. Also there was significant positive correlation between the size of the tumour and stiffness measured by fibroscan. The bigger the size of the tumor, the higher the stiffness. These results were in agreement with Liana et al. **[15]** who stated that LSM was significantly higher in patients with HCC with nodules >50 mm (58.3±18.4 kPa vs32.5±14.3 kPa). Also, the current study showed that there was a significant positive correlation between Okuda classification, CLIP staging with the stiffness measured by fibroscan. The more advanced liver disease (according to each classification), the higher stiffness of fibroscan. This correlation is not discussed by researchers till now. This study found that there was no correlation between VISUM and stiffness measured by fibroscan which is not discussed by researchers till now. Also, this study showed that there was a significant positive correlation between Tokyo classification and stiffness measured by fibroscan which is not discussed by researchers till now.

## CONCLUSION

According to this study, fibroscan has an important role in early detection of HCC in cirrhotic patients with cut off 30.4 Kpa. Cirrhotic patients with liver stiffness ≥30 kpa are most likely to have HCC. Cirrhotic patients with liver stiffness ≥25 kpa need close follow up as they are at high risk to develop HCC.

**Conflict of interest :**
The author declared that he has no competing interests or conflict of interest.

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