Original Article

Comparison between transient elastography and other markers for predicting the fibrosis stages of patients with chronic HCV infection in Beni-Suef governorate, Egypt

Gamal Shiha, Alaa Aboud, Doaa Mahmoud Khalil, Asmaa Salama Sieddek

Summary

Background and aims. *Liver biopsy is the gold standard for diagnosis and staging of liver fibrosis, but it is invasive and has many complications that diminished its practice. Now, robust of non-invasive index for predicting fibrosis is very valuable. The aim of this study is to validate and determine the efficacy of non-invasive markers aspartate aminotransferase to platelet ratio (APRI), FIB4 and AFP versus Fibroscan for predicting the fibrosis stages of patients with chronic HCV infection.* ***Methods:*** *This cross-sectional study included 621 patients with chronic hepatitis C infection attended out-patient clinic (Medical center Beni-Suef branch, the association of liver patient care, ELP, El-Mansoura) for HCV viral hepatitis treatment. The patients were diagnosed by RT-PCR. Sensitivity and specificity of APRI, FIb-4 and AFP were estimated by receiver operator characteristic curve (ROC) for predicting stage of fibrosis versus Fibroscan.* ***Results****: Compared to Fibroscan as standard at value 12 kPa, the sensitivity and specificity of APRI was (67% and 61% and AUC= 0.747), of FIb-4 was (77% and 72% and AUC = 0.769) and of AFP was (77% and 60% and AUC = 0.734) for predicting early stages of fibrosis (F0-F1-F2). However, with advanced liver fibrosis (F3-F4) compared to Fibroscan at value 15 kPa, the sensitivity and specificity of APRI was (100% and 95.3% and AUC= 0.960) and of FIb-4 was (100% and 87.4% and AUC= 0.879) and of AFP were (100% and 51% and AUC= 0.684) for predicting F4 fibrosis.* ***Conclusion****: Given the higher cost and reduced availability of Fibroscan, this study showed that, the non-invasive tests APRI, FIB-4 index and AFP are practically useful markers for diagnosis and monitoring of liver fibrosis among patients with chronic HCV patients especially with advanced liver fibrosis.*

Keywords: *Liver stiffness measurement, Transient elastography, FibroScan, Liver fibrosis, Chronic Hepatitis C*

Medical Journal of Viral Hepatitis
(*MJVH*) 2019; 4 (1) - pp. 45-52

Received: 3/7/2019
Revised: 28/8/2019
Accepted: 4/9/2019
Published Online: 15/11/2019

(Gamal El-Sayed Shiha) Internal Medicine dept., Mansoura Univ.; Egyptian Liver Research Institute and Hospital (ELRIH), Sherbin, El-Mansoura, Egypt
(Alaa Aboud, Asmaa Salama Sieddek) Tropical Medicine dept., Faculty of Medicine, Beni-Suef Univ., Egypt
(Doaa Mahmoud Khalil) Public health and community medicine dept., Faculty of Medicine, Beni-Suef Univ., Egypt.

*** CA:** Asmaa Salama Sieddek
Asmaa.Salama@med.bsu.edu.eg.

Introduction

Hepatitis C virus (HCV) infection is one of the causes of chronic liver disease[1]. Chronic liver diseases increase liver fibrosis with structural and functional alterations as the amount of fibrosis is correlated with the risk of developing complication of cirrhosis and HCC[2]. Diagnosis and treatment of patients with chronic hepatitis mostly rely on the staging of liver fibrosis[3]**.** Liver biopsy is the standard procedure for staging fibrosis internationally[4,5]. On the contrary liver biopsy provides only a small part of the whole organ and this part might not be representative for the amount of hepatic fibrosis in the whole liver due to heterogeneity in its distribution[6]. By using liver stiffness measurement Transient elastography, the liver fibrosis can be staged using 1-dimensional ultrasound TE (FibroScan (R), Echosens, Paris, France)[7]. Advantages of TE include a short procedure time (<5 min), immediate results, and the ability to perform the test at the bedside or in an outpatient clinic. Finally, it is easy procedure can be performed by a nurse or a technician after minimal training (about 100 examinations)[8]. Numerous laboratory tests, and scores, have

been proposed for non-invasive prediction of hepatic fibrosis in chronic HCV-infected patients. Amongst these, aspartate aminotransferase (AST)-to platelet ratio (APRI), and FIB4, are readily available in clinical practice with good accuracy for predicting hepatic fibrosis[9]. Elevated levels of AFP have been revealed to be more frequently associated with chronic liver disease and fibrosis and the value of measuring AFP in HCV has been called into question[10]. The aim of this study is to evaluate the efficacy of non-invasive markers APRI, FIB4 and AFP in comparison to Fibroscan for predicting the fibrosis stages of patients with chronic HCV infection.

Patients and Methods

Study design

This cross-sectional study was conducted at the HCV outpatient clinic (Medical center Beni-suef branch Egyptian liver Hospital, ELP, El-Mansoura) for HCV viral hepatitis treatment. The inclusion criteria were; age older than 18 years and chronic infection by hepatitis C diagnosed by RT-PCR. The exclusion criteria were the presence of ascites, pacemaker or pregnancy, co-infection with HBV or human immunodeficiency virus (HIV), other causes of chronic liver disease and patients with hepatocellular carcinoma.

Laboratory assessment

Routine laboratory assessment was done before the start of treatment including; complete blood picture, aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum albumin, serum bilirubin, prothrombin time (PT), and international normalization ratio (INR), serum creatinine, HBsAg, fasting blood sugar (FBS), Alfa fetoprotein (AFP). Serological analysis Quantitative HCV-RNA count. *The APRI score was calculated using Wai's formula (A)[11]. *The FIB4 score was calculated using Sterling's formula (B)[12].

$$APRI = \frac{(\text{AST/upper limit of normal})}{\text{platelet count (expressed as platelets } (10^9/L) \times 100}$$

$$FIB4 = \frac{\text{Age (years)} \times \text{AST (IU/L)}}{\text{Platelet count } (10^9/L) \times \text{ALT (IU/L)}}$$

Abdominal Imaging

Abdominal and pelvic ultrasonography was done before treatment, to evaluate the signs of liver cirrhosis, hepatic decompensation, portal hypertension and fatty liver.

Transient elastography (TE)

The procedures were performed. The right lobe of the liver was accessed through an intercostal space while the patient was lying down in the dorsal decubitus position with the right arm in maximum abduction position. Using the FibroScan (Echosens 405, Paris, France), a portion of liver of at least 60 mm in thickness, free of large vessels, was identified for exam-ination. The rate of successful measurement was calculated as the ratio between the numbers of validated to total measurements. The results were expressed as a median value of the total measurements in kilo Pascal (kPa). TE was considered reliable when the following 3 criteria had been met: 10 successful measurements, an interquartile range (IQR) lower than 30% of the median value, and a success rate of more than 60%[13]. The cut-off values of the Fibroscan in hepatitis C virus mono-infection were meas-ured according to Ziolet al., 2005[14]:

- F0-F1: 0 - 7 Kpa
- F1-F2: 7 - 8.5 Kpa
- F2: 8.5 - 9.5 Kpa
- F3: 9.5 - 12.5 Kpa
- F3-F4: 12.5 - 14.5 Kpa.

Statistical analysis

Analysis of the data was done by IBM computer using SPSS (statistical package for social science version 22). Data were described as mean ± standard deviation (SD) for quantitative variables. One way ANOVA test was used for comparison of quantitative variable among more than two independent groups. Spearman correlation coefficient (r) test was used to rank different variables against each other either positive or inverse. The probability value (P) <0.05 was considered statistically significant. The receiver operator characteristic (ROC) curve was constructed to obtain the most sen-sitive and specific cut-off for each technique.

Results

Table 1 shows the clinical and demographic characteristics of the participants. The study included 621 patients, 349 males (40.1%) and 375 females (59.9%). Out of 621 patients incl-uded in this study, abdominal ultrasound was normal in 269 patients (43.3%), bright hepatomegaly was found in 177 patients (28.5%) and liver cirrhosis was found in 175 patients (28.2%). Table 2 shows

that, APRI in group A (F0-F1) stage of fibrosis was 0.32±0.22 that was increased at group D (F4) up to 1.01±0.93. While, FIB4 in group A of fibrosis was 0.99± 00.58 that was increased at advanced stage of fibrosis (group D) up to 2.44±1.7. Moreover, AFP level in group A stage of fibrosis was 3.7±3.1that was increased at advanced stage (group D) of fibrosis up to13.02±7.02. Table 3 shows the comparison between early (F0-F2) stages of fibrosis (12 kps) and advanced (F3-F4) stages of fibrosis (15 kps) measured by Fibroscan as regard the value of APRI, FIB 4 scores and AFP level. There was significant increase in APRI, FIB4 scores and AFP level at F3-F4 (advanced fibrosis) versus, early fibrosis (F0-F2). There was a statistically significant positive correlation between Fibroscan and patient criteria as regard, age, AFP, AST, ALT and portal vein diameter (P value was ≤ 0.001 for all) and significant negative correlation with serum albumin (p <0.001) and platelet (p= 0.002). Also there was a statically significant positive correlation between Fib-4 score and the age, AFP, AST, ALT (P value was ≤ 0.001 for all), creatinine (p= 0.004), portal vein diameter (p= 0.009) and WBC (p= 0.004), in addition there was a significant negative correlation with serum albumin and platelet (p <0.001). Furthermore, a statistically significant positive correlation was found between APRI score and patient criteria included AFP, AST, ALT (p <0.001), portal vein diameter (p= 0.003) and significant negative correlation with serum albumin and platelet (p <0.001), tab. (4). Table 5 and figure 1 show the sensitivity, specificity and AUC of AFP, fib-4 and APRI at Fibroscan measurement at 12 kps for diagnosis of liver fibrosis stages. At a cut-off value of 3.97, the sensitivity and specificity of AFP was (77% and 60% respectively). Of FIB 4, at cut-off value of 1.36, the sensitivity and specificity of was (77% and 72% respectively). As regard the APRI at cut-off value of 0.33 the sensitivity and specificity of was (67% and 61% respectively) for diagnosis of fibrosis stages. Table 6 and figure 2 show the sensitivity, specificity and AUC of AFP, fib-4 and APRI at Fibro scan measurement at 15kps for diagnosis of liver fibrosis stages. At a cut-off value of 3.07, the sensitivity and specificity of AFP was (100 % and 51% respectively). Of FIB 4 at a cut-off value of 2.11, the sensitivity and specificity was (100 % and 87.4 % respectively). As regard the APRI, at cut-off value of 1.16 the sensitivity and specificity was (100% and 95.3% respectively) for diagnosis of fibrosis stages.

Table (1) Baseline characteristics of studied patients

Parameters	Mean±SD
Age/ years	48.05±13.30
Fasting blood sugar (mg/dl)	97.51±41.06
AFP (ng/ml)	4.92±7.29
Albumin (g/dl)	4.09±0.51
Creatinine	0.82±0.20
Total Bilirubin (mg/dl)	0.72±0.27
AST (U/ L)	36.60±26.20
ALT (U/ L)	41.28±27.84
Hemoglobin g/dl)	13.59±1.61
Platelat count (cmm^3)	26.40±10.06
WBC (cmm^3)	6.66±12.16
Fibroscan (kps)	7.44±5.96
Fib -4 score	1.21±0.89
APRI score	0.42±0.43

Data were presented as mean± SD. ***AFP****, α-fetoprotein;* ***ALT****, alanine aminotransferase;* ***AST****, aspartate aminotransferase;* ***WBCs****, white blood cells;* ***APRI****, aspartate aminotransferase (AST) to platelet Ratio Index.*

Table (2) Comparison between the stages of fibrosis measured by Fibroscan regarding the APRI, FIB 4 and AFP scores.

Variables	**Group A (F0-F1)**	**Group B (F2)**	**Group C (F3)**	**Group D (F4)**
APRI score	0.22.32±00	0.43±0.28	0.63±0.51	1.01±0.93
P-value	**≤0.001 for all stages**			

FIB4 score	0.99±0.58	1.28±0.62	1.72±0.97	2.44±1.7
P-value	**≤0.001 for all stages**			
AFP	3.7±3.1	5.6±5.5	6.34±5.05	13.02±7.02
P-value	**≤0.001 for all stages**			

Table (3) Comparison between early and advanced stages of fibrosis measured by Fibroscan regarding the APRI, FIB 4 scores and AFP.

Variables	Group A (F0- F2)	Group B (F3 -F4)	P-value
APRI score	0.34±0.23	0.82±0.71	<0.001
FIB4 score	1.03±0.58	2.07±1.41	<0.001
AFP	4.6±3.9	13.4±9.5	<0.001

Table (4) Correlation between Fibroscan, APRI and FIB4 scores and patient criteria using Pearson Correlation.

	Fibroscan (kps)		Fib-4 score		APRI score	
	r	p	r	p	r	p
Age/years	0.220	<0.001	0.443**	<0.001	0.094	0.062
Fasting blood sugur (mg/dl)	0.053	0.487	0.085	0.273	0.038	0.625
AFP (ng/mL)	0.393**	<0.001	0.291**	<0.001	0.234**	<0.001
Albumin (g/dl)	-0.249**	<0.001	-0.266**	<0.001	-0.240**	<0.001
Creatinine	0.088*	0.034	0.151**	0.004	0.122*	0.018
Total Bilirubin (mg/dl)	0.079	0.055	0.130*	0.012	0.154**	0.003
AST (U/L)	0.315**	<0.001	0.639**	<0.001	0.776**	<0.001
ALT (U/L)	0.243**	<0.001	0.475**	<0.001	0.739**	<0.001
Hemoglibin (g/dl)	0.014	0.731	0.071	0.163	0.124*	0.014
Platelets(cmm^3)	-0.012**	0.002	-.0473**	<0.001	-0.408**	<0.001
WBC (cmm^3)	-0.025	0.539	-0.146**	0.004	-0.122*	0.015
Portal_vien diameter (mm)	0.220**	<0.001	0.131**	0.009	0.150**	0.003

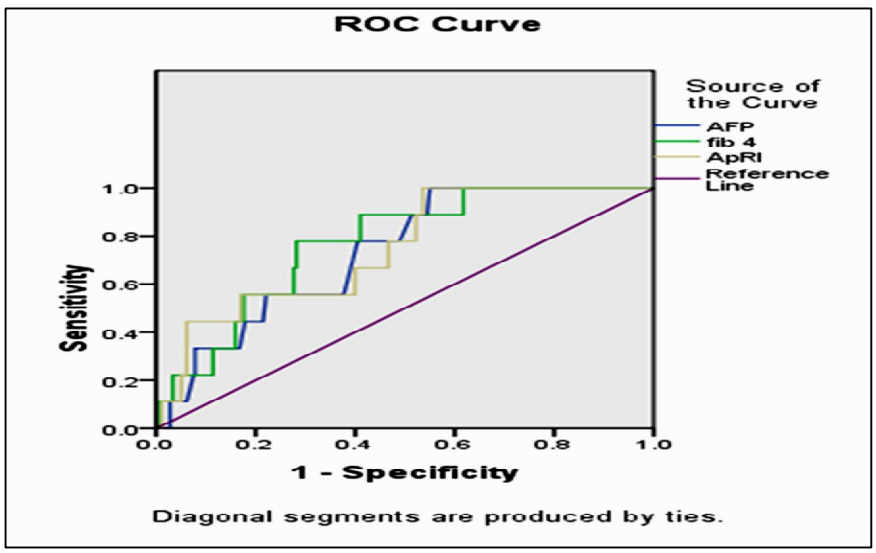

Figure (1) Receiver operating characteristic curves of AFP, FIB-4 and APRI at Fibro scan measurement at 12 kps.

Table (5) Level and area under ROC of AFP, FIB-4 and APRI for detection liver fibrosis stage at Fibroscan measurement at 12kps.

Predictor variables	Cut off points	Area under the curve	Sensitivity	Specificity
AFP	3.97	0.734	77%	60%
FIB 4	1.36	0.769	77%	72%
APRI	0.33	0.747	67%	61%

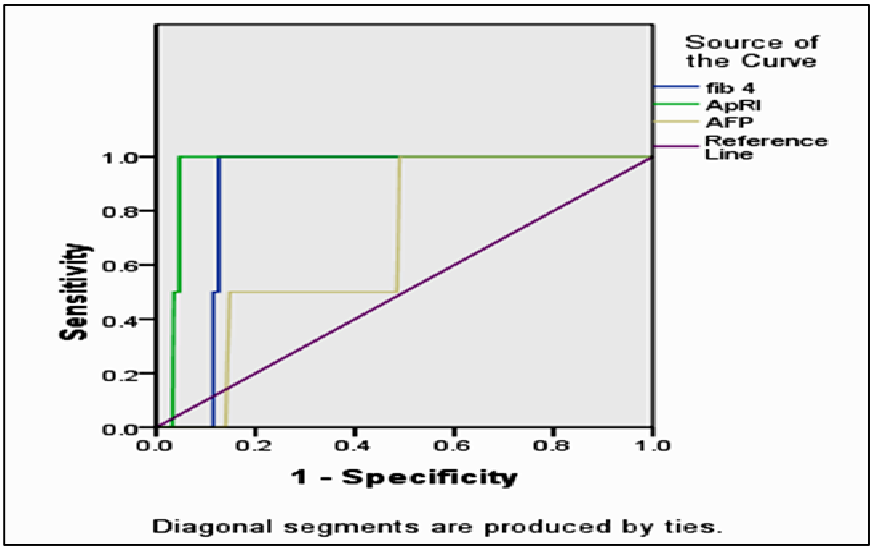

Figure (2) Receiver operating characteristic curves of AFP, fib-4 and APRI at Fibro scan measurement at 15kps.

Table (6) Level and area under ROC of AFP, FIB-4 and APRI for detection liver fibrosis stage at Fibroscan measurement at 15kps.

Predictor variables	Cut off points	Area under the curve	Sensitivity	Specificity
AFP	3.07	0.684	100%	51%
FIB 4	2.11	0.879	100%	87.4%
APRI	1.16	0.960	100%	95.3%

Discussion

Assessment of the liver fibrosis is essential step in management and follow up of patients with HCV viral hepatitis[15]. A lot of research has been done for evaluating non-invasive methods to determine liver fibrosis[16,17]. Serum biomarkers can be used as an alternative to liver biopsy for the staging of liver fibrosis to guide treatment regime and follow up of patient, screening of varices and hepatocellular carcinoma. In this, we compared the accuracy of the serum biomarker, APRI, FIB4 and AFP assay in predicting fibrosis, using LSM by TE as reference. This was done because TE more accurately detects cirrhosis and significant fibrosis[18]. In this study we assessed the liver fibrosis used LSM by TE (fibroscan) as reference compared to the accuracy of the serum biomarker APRI,FIB4 and AFP for evaluation of liver fibrosis in HCV patients who treated in our clinic. When Fibroscan measurement at 12 kps, AFP at Cut off value 3.97 shows, 77% sensitivity and 60% specificity whereas,Fib4 score at Cut off value 1.36 shows, 77% sensitivity and 72% specificity and APRI score at Cut off value 0.33 shows, 67% sensitivity and 61% specificity. In agreement with this study, Vallet-Pichardet al evaluated the use of FIB-4 index in 847 patients with HCV mono-infection; the study demonstrated that, FIB-4 index <1.45 had a negative predictive value of 94.7% to exclude severe fibrosis with a sensitivity of 74.3%[19]. On other side, Sumida et al evaluated the use of FIB-4 in 576 patients with nonalcoholic fatty liver disease; found that FIB-4 index <1.45 had a negative predictive value of 98% to exclude severe fibrosis with a sensitivity of 90% and specificity of 64%[20]. While in patients with advanced fibrosis (Fibroscan measurement 15 kps) that matched F4 fibrosis, AFP at Cut off value 3.07 shows 100% sensitivity and 51% specificity, Fib4 score at Cut off value 2.11 shows 100% sensitivity and 87% specificity and APRI score at Cut off value 1.16 shows 100% sensitivity and 95% specificity. So APRI and FIB-4 score are useful in patient with advanced fibrosis, that was in agreement with study of Gökcan et al, that found the ability of APRI and FIB-4 tests to determine mild fibrosis and more accuracy in determi-

nation of advanced fibrosis (F4)[21]. Moreover, El Nakeeb et al, found that, the FIB-4 index proved to be sensitive and specific in differentiation between patient with no or significant fibrosis (Metavir F0-F3) and patients with cirrhosis) with the best cut-off value at 1.88 where sensitivity was 84.6% and specificity was 88.2%[22]. There was a statistically significant elevation of FIB-4 index with more liver fibrosis where is, Fib4 score at (12 Kpas) was 1.366 that was increased to 2.11 at (15 Kpas). This was in agreement with Sumida et al, who found a statistically significant elevation of APRI Score with more progression of liver fibrosis, from 0.33 at (12 Kpas) that increased to 1.16 (at 15 Kpas)[23]. In this study at fibroscan value 15 Kpas (F4), APRI score has shown higher specificity (95%) as compared to FIB4 (87%). This is in accordance with study that showed that, APRI has shown higher sensitivity (91.2%) as compared to FIB4 (73.6%) but had lowered specificity (32.4% vs 68.3%)[24]. In our study, the sex is not independently associated with HCV related hepatic fibrosis. A similar result was reported by Hishamet al[25]. In this study LSM by TE suggests that age, AST, ALT,AFP have a significant impact on fibrosis. A similar result was reported by Orasan et al[26]. In this study, when comparing APRI score and FIB4 score with different stage of fibrosis measured by fibroscan, we found, a statistically significant increase from early fibrosis stage (F1- F2) to advanced fibrosis stage (F3-F4), these results matched that of Sumida et al[23]. In our study we found a statistically significant positive correlation between Fibroscan and patient criteria as regard, age, AFP, AST, ALT and portal vein diameter and significant negative correlation with serum albumin and platelet. Also there was a statically significant positive correlation between Fib-4 score and the age, AFP, AST, ALT, creatinine, portal vein diameter, in addition a significant negative correlation with serum albumin and platelet. Furthermore, a statistically significant positive correlation was found between APRI score and patient criteria included AFP, AST, ALT, portal vein diameter and significant negative correlation with serum albumin and platelet. In the contrary, El Nakeeb[22], found no statistically significant correlation as regard the gender, ALT, and apha fetoprotein. In this study platelet has negative correlation with fibroscan, Fib-4 and APRI score. Possible explanations for these correlations are Platelet count is known to correlate with the amount of portal hypertension and advanced fibrosis[27]. Portal vein diameter has statistically significant positive correlation with fibroscan, Fib-4 and APRI score. This was in agreement with study that compares and correlate FibroScan values with gray scale sonographic assessment of portal vein diameter and found variation of calibre of portal vein is a good indicator of moderate to severe fibrosis[28]. Our study shows a significant increase in APRI, FIB-4 and AFP levels with progression of fibrosis from mild fibrosis (F0-F1) stage to cirrhosis (F4) stage. This result was in agreement with the results of other study[24].

Conclusion

The APRI, FIB-4 index and AFP are non-invasive test for diagnosis and monitoring of liver fibrosis among patients with chronic HCV infection. Our study showed that, these non-invasive tests are practically useful markers for diagnosis and monitoring of liver fibrosis among patients with chronic HCV patients specially with advanced liver fibrosis.

List of abbreviations

ALT, alanine transaminase
AST, aspartate transaminase
AUC, area under receiver operator characteristic curve
CHC, chronic hepatitis C
Hgb, hemoglobin
IQR, inter quartile range
kPa, kilo pascal
LSM, liver stiffness measurement
TE, transient elastography
WBCs, white blood cells
APRI, aspartate aminotransferase (AST) to platelets ratio Index
PCR, polymerase chain reaction
PPV, positive predictive value
NPV, negative predictive value
ROC, receiver operator curve.

References

1- Lavanchy D. Evolving epidemiology of hepatitis C virus. **Clin Microbiol Infec**. 2011; 17: 107-115.

2- Yano M, Kumada H, Kage M, Ikeda K, Shimamatsu K, Inoue O, et al. The long-term pathological evolution of chronic hepatitis C. **Hepatology.** 1996; 23: 1334-1340.

3- Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. **Hepatology.** 1996; 24: 289-293.

4- EASL clinical practice guidelines: Management of chronic hepatitis B. **J. Hepatol.** 2009; 50: 227-242.

5- Ghani M, Strader D, Thomas D, Seef L. Diagnosis, management and treatment of hepatitis C: An update. **Hepatology.** 2009; 49: 1335-1374.

6- Regev A, Berho M, Jeffers L, Milikowski C, Molina E, Pyrsopoulos N, et al. Sampling error and inter-observer variation in liver biopsy in patients with chronic HCV infection. **Am J Gastroentero**l. 2002; 97: 2614-2618.

7- Sandrin L, Fourquet B, Hasquenoph J, Yon S, Fournier C, Mal F, et al. Transient-elastography: A new non-invasive method for assessment of hepatic fibrosis. **Ultrasound Med Biol.** 2003; 29: 1705-1713.

8- Boursier J, Konate A, Guilluy M, Gorea G, Sawadogo A, Quemener E, et al. Learning curve and inter-observer reproducibility evaluation of livers tiffness measurement by transient elastography. **Eur J. Gastroenterol Hepatol**. 2008; 20: 693-701.

9- Rosenberg W, Voelker M, Thiel R. Serum markers detect the presence of liver fibrosis: A cohort study. **Gastroenterology.** 2004; 127: 1704-1713.

10- Di Bisceglie A, Sterling R, Chung R. Serum alpha-fetoprotein levels in patients with advanced hepatitis C: Results from the HALT-C trial**. J. Hepatol.** 2005; 43 (3): 434-441

11- Wai C, Greenson J, Fontana R. A simple non-invasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. **Hepatology.** 2003; 38: 518-526.

12- Sterling R, Lissen E, Clumeck N. Development of a simple non-invasive index to predict significant fibrosis inpatients with HIV/HCV co-infection**. Hepatology.** 2006; 43: 1317-1325.

13- Poynard T, Ingiliz P, Elkrief L, Munteanu M, Lebray P, Morra R, et al. Concordance in a world without a gold standard: A new noninvasive methodology for improving accuracy of fibrosis markers. **PLoS ONE.** 2008; 3: e3857.

14- Ziol M, Handra-Luca A, Kettaneh A. Non-invasive assessment of liver fibrosis by measurement of stiffness in patients with chronic hepatitis C. **Hepatology.** 2005: 41, 48-54.

15- Wai C, Greenson J, Fontana R, Kalbfleisch J, Marrero J, Conjeevaram H, et al. A simple non-invasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. **Hepatology.** 2003; 38: 518-526.

16- Friedrich-Rust M, Ong M, Martens S, Sarrazin C, Bojunga J, Zeuzem S, et al. Performance of transient elastography for the staging of liver fibrosis: A meta-analysis. **Gastroenterology.** 2008; 134: 960-974.

17- Abdollahi M, Pouri A, Ghojazadeh M, Estakhri R, Somi M. Non-invasive serum fibrosis markers: A study in chronic hepatitis**. Bioimpacts.** 2015; 5: 17-23.

18- Castera L. Non-invasive methods to assess liver disease in patients with hepatitis B or C. **Gastroenterology.** 2012; 142: 1293-1302.

19- Vallet-Pichard A, Mallet V, Nalpas B, Verkarre V, Nalpas A, Dhalluin-Venier, V, et al. FIB-4, an inexpensive and accurate marker of fibrosis in HCV infection: Comparison with liver biopsy and fibro test. **Hepatology.** 2007; 46, 2-36.

20- Sumida Y, Yoneda M, Hyogo H, Itoh Y, Ono M, Fujii H, et al. Validation of the FIB4 index in a Japanese nonalcoholic fatty liver disease population. **BMC Gastroenterology.** 2012: 12, 2.

21- Hale G, Ufuk Barış K, Erkin Ö, Fatih S, Derya Ö, Nuretdin S, et al. The predictive value of non-invasive serum markers of liver fibrosis in patients with chronic hepatitis C. **Turk J. Gastroenterol.** 2016; 27: 156-164.

22- El Nakeeb N, Helmy A, Saleh S, Abdellah H, Abdel Aleem M, Elshennawy D, et al. Comparison between FIB-4 index and fibroscan as marker of fibrosis in chronic HCV infection in Egyptian patients. **Open J. of Gastroenterology.** 2014: 4, 383-391.

23- Sumida Y, Yoneda M, Hyogo H, Itoh Y, Ono M, Fujii H, et al. Validation of the FIB4 index in a Japanese non-alcoholic fatty liver disease population. **BMC Gastroenterology.** 2012, 12, 2.

24- Taneja S, Tohra S, Duseja A, Dhiman R, Chawla Y, et al. Non-invasive assessment of liver fibrosis by transient elastography and FIB4/APRI for prediction of treatment response in chronic hepatitis C: An experience from a tertiary care hospital. **J. Clin Exp Hepatol.** 2016; 6 (4): 282-290.

25- Dabbous H, El-Folly R, EL-Nakeeb H, Helmy A, Saleh S, et al. Evaluation of the Role of Alpha-Fetoprotein (AFP) Levels in Chronic Viral Hepatitis C Patients, Without Hepatocellular Carcinoma (HCC**). JMSCR**. 2015; 3(3); 4787-4800.

26- Orasan H, Iancu M, Sava M, Saplontai-Pop A, Cozma A, Sarlea S, et al. Non-invasive assessment of liver fibrosis in chronic viral hepatitis. **Eur J. Clin Invest.** 2015; 45: 1243-1251.

27- Sterling, K, Stravitz, T, Luketic A, Sanyal J, Contos J, Mills S, et al. A comparison of the spectrum of chronic hepatitis C virus between Caucasians and African Americans. **Clinical Gastro-enterology and Hepatology.** 2004; 2, 469-473.

28- Yayati P, Akhilesh R. Liver fibrosis assessment: A correlation of fibro scan values with gray scale assessment of portal vein. **Int J Res Med Sci.** 2018; 6 (1): 317-320.