Received: 15 May 2017 | Revised: 9 December 2017 | Accepted: 10 December 2017
DOI: 10.1002/jmv.25026

RESEARCH ARTICLE

WILEY JOURNAL OF MEDICAL VIROLOGY

Novel scores combining AFP with non-invasive markers for prediction of liver fibrosis in chronic hepatitis C patients

Mohamed Gamil[1] | Mohamed Alboraie[2] | Mohammad El-Sayed[3] | Aisha Elsharkawy[3] | Noha Asem[4] | Tamer Elbaz[3] | Mohammad Mohey[3] | Bahaa Abbas[5] | Mai Mehrez[1] | Gamal Esmat[3]

[1] National Hepatology and Tropical Medicine Research institute, Cairo, Egypt

[2] Department of Internal Medicine, Al-Azhar University, Cairo, Egypt

[3] Department of Endemic Medicine and Hepatology, Cairo University, Cairo, Egypt

[4] Department of Public Health and Community Medicine, Cairo University, Cairo, Egypt

[5] Military Medical Academy, Cairo, Egypt

Correspondence
Mohammad El-Sayed, MD, Department of Endemic Medicine and Hepatology, Cairo University, Cairo 11562, Egypt.
Email: mohammadelsayed76@yahoo.com

Serum levels of alpha-fetoprotein (AFP) were reported to increase in patients with significant or advanced hepatic fibrosis. Combination of non-invasive tests decreases the use of liver biopsy in large proportion of chronic HCV patients. The aim of the study was to compare and combine AFP with commonly used non-invasive fibrosis tests in novel scores for prediction of different stages of hepatic fibrosis. Six hundred and fifty two treatment naïve chronic hepatitis C patients were enrolled. Demographic data, basic pre-treatment laboratory tests including complete blood count (CBC), liver biochemical profile and renal functions test, international normalized ratio (INR) in addition to AFP, liver stiffness measurement (LSM) by Fibroscan and liver biopsies were retrospectively analyzed. AST to Platelet Ratio Index (APRI) and FIB-4 scores were calculated. Different predictive models using multivariate logistic regression analysis were generated and presented in equations (scores) composed of a combination of AFP, LSM plus FIB-4/APRI scores. AFP was correlating significantly with LSM, FIB-4, and APRI scores. Areas under receiver operating characteristic curves (AUROCs) for predicting significant hepatic fibrosis, advanced hepatic fibrosis, and cirrhosis were 0.897, 0.931, and 0.955, respectively, for equations (scores) containing AFP, LSM, and FIB-4. AUROCs for predicting significant hepatic fibrosis, advanced hepatic fibrosis and cirrhosis were 0.897, 0.929, and 0.959, respectively, for equations (scores) containing AFP, LSM, and APRI. The study shows that combining AFP to serum biomarkers and LSM increases their diagnostic performance for prediction of different stages of liver fibrosis.

KEYWORDS
AFP, fibrosis, HCV, novel scores

1 | INTRODUCTION

Alpha-fetoprotein (AFP) is an alpha 1 globulin that constitutes most of the serum proteins of the fetus.[1] It is encoded by AFP gene[2] and produced by many tissues including fetal liver, yolk sac, and gut in human and other different species.[3,4] AFP was first discovered in 1956 by Halbrecht and Klibanski[5] in hepatocellular carcinoma (HCC) and other tumors,[6–8] maternal serum during pregnancy[9] adverse pregnancy outcomes,[10] neural tube defects,[11] and Down's syndrome.[12] AFP serum levels were elevated in acute and chronic HCV especially in presence of steatosis and fibrosis.[13–18] Different non invasive fibrosis markers are used currently with good acceptability, reliability, and reproducibility.[19] APRI and FIB-4 are two routinely available scores for prediction of hepatic fibrosis.[20,21] They were validated in different

chronic liver diseases including chronic HCV with good sensitivity and specificity.[22] Fibroscan is a highly accurate method for assessment of hepatic fibrosis with good sensitivity and specificity.[23] AFP has been involved in many surrogate biochemical scores for prediction of different stages of hepatic fibrosis.[24–26] The aim of the study was to compare AFP with commonly used non-invasive fibrosis tests and to combine AFP with these tests in novel scores for prediction of different stages of hepatic fibrosis.

2 | PATIENTS AND METHODS

Data of 652 chronic HCV naïve patients was collected from Kasr Al-Ainy viral hepatitis treatment center in Cairo University and retrospectively analyzed. Patients were classified according to fibrosis stage in pre-treatment liver biopsy into five groups according to METAVIR score (F0, F1, F2, F3, and F4). The following pre-treatment investigations were done for the patients including liver biochemical profile (ALT, AST, serum albumin, total bilirubin), PT, PC, INR, urea, creatinine, CBC, AFP, HCV Ab, PCR for HCV RNA, HBsAg, abdominal ultrasound, Fibroscan® and liver biopsy. Patients were divided into three groups: (i) Patients with significant hepatic fibrosis (≥F2); (ii) Patients with advanced hepatic fibrosis (≥F3); (iii) Patients with liver cirrhosis (F4). Patients with other type of chronic liver disease or hepatocellular carcinoma were excluded from the study. We calculated (APRI) and FIB-4 scores according to their formulas.[20,21]

2.1 | Liver stiffness measurement (LSM)

LSM was done using ultrasound Transient Elastography (Fibroscan® 502, Echosens, France). LSM was obtained in fasting patients (at least 4 h) 1 week before liver biopsy, and the examination was done by the technique described by Castera. Quality criteria included 10 valid measurements and the ratio interquartile range on median (IQR/median) < 30%. Cutoff values for (≥F2), (≥F3), and (F4) were 7.1, 9.5, and 12.5 KPa, respectively.[27]

2.2 | Serum biomarkers[20,21]

Calculation of APRI and FIB-4 scores was done as follows:

APRI = (AST/AST upper limit of normal)/platelet count (expressed as platelets × 10^9/L) × 100.

FIB-4 = Age (years) × AST (U/L)/platelet count (×10^9/L) × ALT (U/L)$^{1/2}$

2.3 | Statistical analysis

Data analysis was performed using SPSS 21 for Windows. Numerical variables were described as mean and standard deviation (SD) and categorical variables were described as numbers (No.) and percentage (%). ROC curves were graphed to determine appropriate AFP levels in predicting different stages of liver fibrosis. Binary Spearman correlation test was used. Scatter diagrams were also graphed to visualize the relation between numerical variables. Results of univariate analysis as well as background literature guided the selection of variables considered for logistic regression modeling (multivariate analysis). Different predictive models using multivariate logistic regression analysis were generated. The best fitting models were composed of a combination of AFP, LSM plus FIB-4/APRI scores. These variables were presented in equations (novel scores) for logit probability of fibrosis stages. Then, ROC curves were graphed for the calculated scores to decide cutoff points that show optimal sensitivity and specificity for significant fibrosis, advanced fibrosis, and cirrhosis.

3 | RESULTS

The study included 652 naïve chronic HCV patients (203 females, 449 males), mean age ± SD was 41 (±10). General characteristics of the studied group are presented in Table 1. According to staging of hepatic fibrosis, we had F0 in 25 patients (3.83%), F1 in 331 patients (50.77%), F2 in 127 patients (19.48%), F3 in 94 patients (14.42%), and F4 in 75 patients (11.50%). AFP could predict significant hepatic fibrosis (≥F2) with 71.3% sensitivity and 62.4% specificity at a cutoff value of 2.55 ng/mL and AUROC curve of 0.743. For advanced hepatic fibrosis (≥F3) and cirrhosis (F4); sensitivity, specificity, and AUROC curve were (69.8%, 77.6%, and 0.79) and (64%, 85%, and 0.818) at cutoff values of 4 ng/mL and 6 ng/mL, respectively.

Cutoff values for AST, AFP, and platelets for prediction of different fibrosis stages taking METAVIR score as a reference one time and LSM by fibroscan as a reference another time are shown in (Supplementary Tables S1 and S2).

TABLE 1 General characteristics of the studied group

	Mean	±SD	Median
Age	41.1	10.6	41
Body mass index (BMI)	27.89	4.45	27.97
(ALT) (U/L)	55.9	42.59	42
(AST) (U/L)	49.5	33.59	39
(GGT) (U/L)	39	36.6	23
Albumin (gm/dL)	3.9	0.5	3.9
Total bilirubin (mg/dL)	0.9	0.27	1
Platelet count (×10^3/mm^3)	212.68	69.59	205
Prothrombin concentration (%)	89.36	9.24	90
Creatinine (mg/dL)	0.97	0.20	0.9
Fasting blood sugar (mg/dL)	92.9	18.6	90
Hemoglobin (gm/dL)	14	1.48	14
Total leucocytic count (×10^3/mm^3)	6.3	1.99	6
(AFP) (ng/mL)	5.16	10	2.73
LSM (Kpa)	9.8	8.1	6.9
FIB-4	1.5	1.19	1.3
APRI	0.70	0.76	0.6

SD, standard deviation.

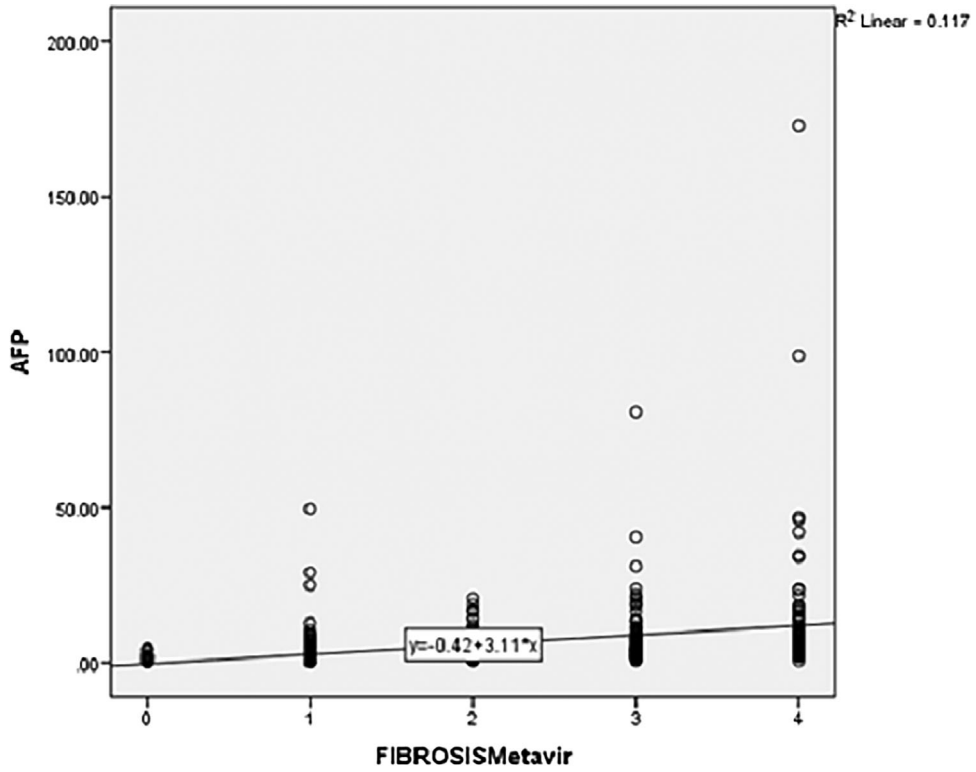

FIGURE 1 Correlation between AFP and different fibrosis stages by METAVIR

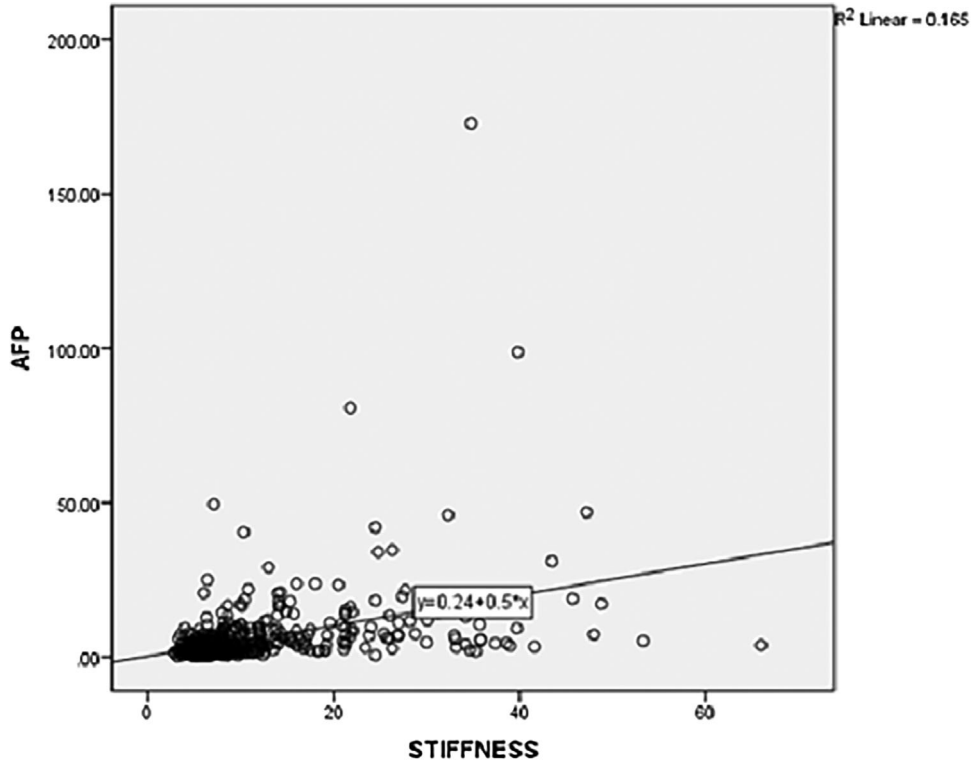

FIGURE 2 Correlation between AFP and liver stiffness measurement (LSM)

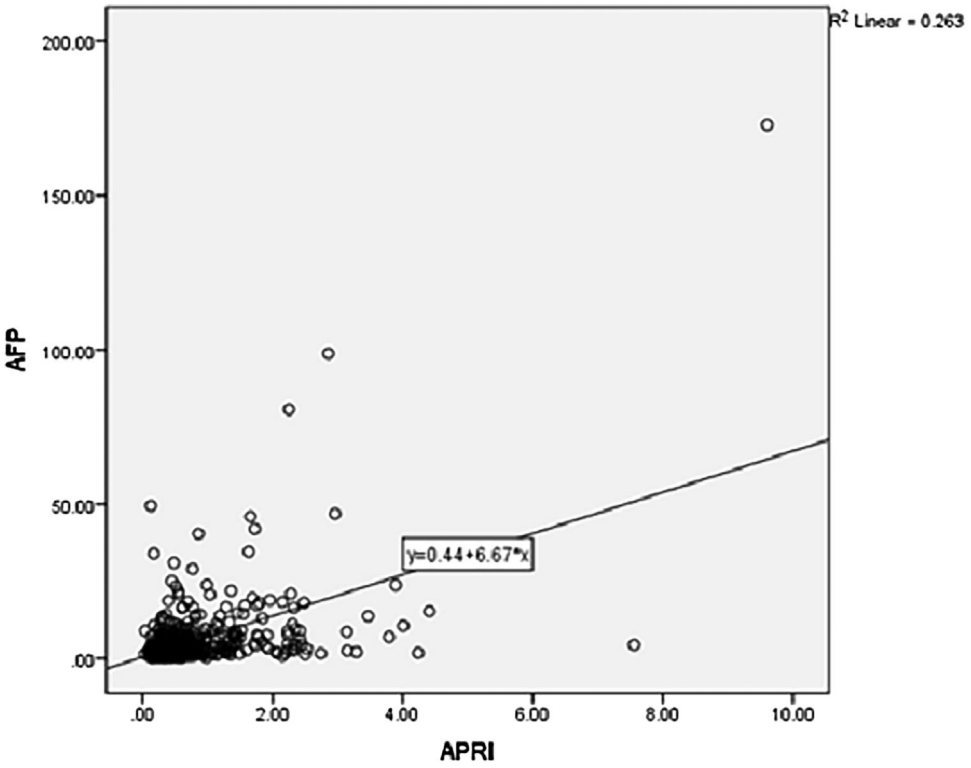

FIGURE 3 Correlation between AFP and APRI

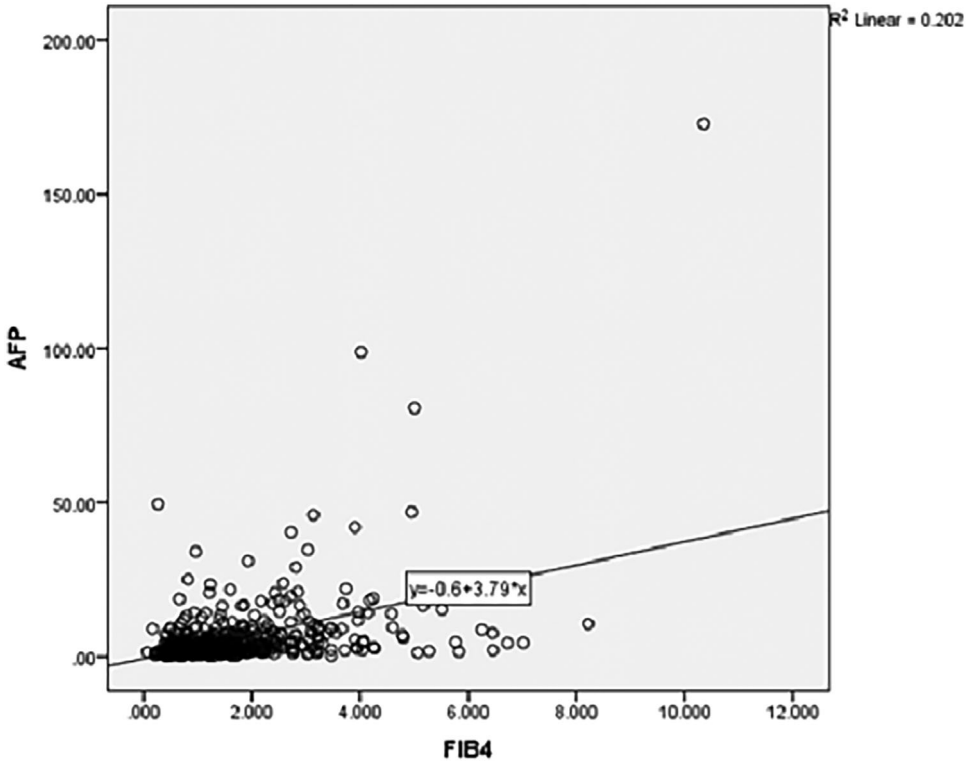

FIGURE 4 Correlation between AFP and FIB-4

TABLE 2 Novel scores for prediction of significant fibrosis, advanced fibrosis, and cirrhosis

	AFP, FIB4, Stiffness	AFP, APRI, Stiffness
Significant fibrosis	L.P. = −4.424 + .055 * AFP + .474 * stiffness	L.P. = −4.362 + .057 * AFP + .503 * stiffness
Advanced fibrosis	L.P. = −5.317 + .042 * AFP + .302 * FIB4 + .370 * stiffness	L.P. = −5.190 + .049 * AFP + .404 * stiffness
Cirrhosis	L.P. = −5.423 + .410 * FIB4 + .190 * stiffness	L.P. = −5.371 + .778 * APRI + .192 * stiffness

Mean values ± SD for LSM in different stages of hepatic fibrosis and cirrhosis were: (4.8 ± 1.2 Kpa for F0), (6.2 ± 2.6 Kpa for F1), (8.3 ± 2.8 Kpa for F2), (13.7 ± 9.2 Kpa for F3), and (25 ± 10.3 Kpa for F4). Calculated biomarker scores in different stages of hepatic fibrosis and cirrhosis showed mean values ± SD of (0.40 ± 0.22 for F0), (0.50 ± 0.41 for F1), (0.64 ± 0.48 for F2), (0.89 ± 0.65 for F3), and (1.63 ± 1.54 for F4) for APRI and (1 ± 0.611 for F0), (1.11 ± 0.78 for F1), (1.41 ± 0.83 for F2), (2.06 ± 1.24 for F3), and (3.00 ± 1.74 for F4) for FIB-4, respectively.

AFP was correlating significantly with stages of hepatic fibrosis by METAVIR, LSM by fibroscan, APRI, and FIB-4 in different stages of hepatic fibrosis and cirrhosis (Figures 1-4)

Novel scores (models) for logit probability of significant, advanced fibrosis and cirrhosis) are shown in Table 2.

AUROC, cutoff values that show optimal sensitivity, specificity and accuracy, PPV and NPV for scores containing AFP, LSM, FIB-4/APRI, in comparison to LSM by fibroscan, APRI and FIB-4 for prediction of significant, advanced fibrosis and cirrhosis are shown in Tables 3-5, respectively.

4 | DISCUSSION

AFP is linked mainly to the presence of HCC although a lot of evidence supports its diagnostic ability for other conditions.[1,4,7–9,11,12,14,16–18] The relation between serum elevation of AFP and liver fibrosis progression was established specially in chronic HCV.[28] Our results showed significant positive correlation between serum levels of AFP and stage of hepatic fibrosis by METAVIR score. These results agree with results of Attallah et al, who found highly significant positive correlation between AFP serum levels and stage of hepatic fibrosis in chronic HCV patients without HCC,[29] Tai et al who found that AFP levels ≥ 6 ng/mL were associated with advanced hepatic fibrosis[30] and Hu et al who found that elevated AFP was associated with advanced hepatic fibrosis in chronic HCV patients.[28] The results showed that the ability of AFP in detection of different fibrosis stages was almost superior to AST and platelets with higher sensitivity and specificity when using METAVIR or fibroscan results as a reference.

There was a significant positive correlation between serum levels of AFP and LSM measured by fibroscan. This was reported in hepatitis B patients by Fung et al, who found that LSM correlated positively with AFP serum levels.[31]

Almost, this is the first study describing such positive correlation between serum levels of AFP and LSM in chronic HCV patients. We also found that serum AFP levels were positively correlating with serum biomarkers of hepatic fibrosis (APRI and FIB-4). Some studies investigated the elevation of AFP in chronic HCV patients without HCC. Chen et al, found that hepatic fibrosis (≥F2), AST ≥40 IU/L, albumin <3.5 gm/dL were significantly associated with elevated AFP.[14] Chen et al, found that old age, thrombocytopenia, elevated AST, and hepatic fibrosis (≥F3) predisposed patients with chronic HCV to have high AFP serum levels.[32]

Increased AFP in chronic HCV patients may be due to a selective transcriptional activation of AFP gene,[33] or it may be related to the process of hepatocyte proliferation or loss of normal architectural arrangement.[34]

In our study, different predictive models using multivariate logistic regression analysis were generated to predict different fibrosis stages. The best fitting models were composed of combination of AFP, LSM plus FIB-4/APRI scores and presented in equations (novel scores) for logit probability of significant fibrosis, advanced fibrosis, and cirrhosis.

AUROCs for hepatic fibrosis ≥F2, ≥F3, and F4 were 0.897, 0.931, and 0.955, respectively, for scores containing AFP, LSM, and FIB-4. Sensitivity and specificity of the optimal cutoff levels at the previous fibrosis groups were 86.5% and 80.2 %, 90.5%, and 84%, 94.7%, and 91.7%, respectively.

AUROCs for hepatic fibrosis ≥F2, ≥F3, and F4 were 0.897, 0.929, and 0.959, respectively, for scores containing AFP, LSM, and APRI. Sensitivity and specificity of the optimal cutoff levels at the previous fibrosis groups were 87.5% and 83%, 89%, and 84%, 93.3%, and 91.6%, respectively.

Previous studies developed three scores combining AFP with other serum biomarkers to predict different hepatic fibrosis stages in

TABLE 3 Cutoff values of the novel scores in comparison to LSM by Fibroscan, APRI, and Fib-4 for prediction of significant hepatic fibrosis (≥F2)

	Cutoff value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Overall accuracy	AUROC
LSM by fibroscan (kPa)	7.1	85.5	86	82.20	87.50	84.96	0.895
APRI	0.5	60	65	59.21	66.08	62.85	0.704
FIB-4	1.05	74	60	61.17	72.79	66.30	0.739
AFP, FIB4, stiffness	0.330	86.5	80.2	79.01	87.30	83.10	0.897
AFP, APRI, stiffness	0.335	87.5	83	81.45	88.65	85.09	0.897

TABLE 4 Cutoff values of the novel scores in comparison to LSM by Fibroscan, APRI, and Fib-4 for prediction of advanced hepatic fibrosis (≥F3)

	Cutoff value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Overall accuracy (%)	AUROC
LSM by fibroscan (kPa)	9	82.8	89.4	73.10	94.42	87.91	0.929
APRI	0.7	59.2	79.4	50.76	84.63	74.30	0.753
FIB-4	1.45	71.6	75.3	51.05	88.12	74.41	0.802
AFP, FIB4, stiffness	0.168	90.5	84	67.40	96.12	85.92	0.931
AFP, APRI, stiffness	0.165	89	84	66.96	95.48	85.56	0.929

TABLE 5 Cutoff values of the novel scores in comparison to LSM by Fibroscan, APRI, and Fib-4 for prediction of Cirrhosis (F4)

	Cutoff value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Overall accuracy (%)	AUROC
LSM by fibroscan (kPa)	12.2	92	99.01	57.02	98.85	91.01	0.956
APRI	1	60	89.5	40.91	94.40	85.29	0.808
FIB-4	2	70.7	84	36.81	95.57	82.37	0.840
AFP, FIB4, stiffness	0.111	94.7	91.7	59.66	99.23	91.86	0.955
AFP, APRI, stiffness	0.110	93.3	91.6	59.32	99.05	91.77	0.959

chronic HCV patients. Atallah et al created a predictive score (Fibrosis Routine Test [FRT]) consisting of age, AFP, APRI, and albumin. AUROCs were 0.81, 0.89, and 0.95 for hepatic fibrosis ≥F2, ≥F3, and F4, respectively, higher than AUROCs of other fibrosis scores (APRI, FIB-4, GUCI). The sensitivity and specificity of the optimal cutoff levels of hepatic fibrosis ≥F2, ≥F3, and F4 were 73% and 83%, 71% and 83%, 73% and 81%, respectively.[24] Omran et al, created Fibro-α score. It was composed of AFP, AST, ALT, platelet count and used for patients with hepatic fibrosis (≥F3) and (F4). The AUROCs of Fibro-α score were 0.82 for patients with hepatic fibrosis ≥F3 and 0.80 for cirrhotic patients. The sensitivity and specificity of the optimal cutoff levels were 83% and 55% for hepatic fibrosis ≥F3, 82% and 62% for cirrhosis.[25]

Atallah et al, constructed the Biotechnology Research Center (BRC) score combining Age, AFP, and platelet count to stage liver fibrosis. BRC produced AUROCs 0.85 for hepatic fibrosis (≥F2), 0.82 for hepatic fibrosis (≥F3), and 0.88 for F4. The sensitivity and specificity of the optimal cutoff levels for the previous fibrosis groups were 78% and 78%, 74% and 76%, 84% and 80%, respectively.[26]

These findings show that scores of this study are superior to the scores of the previous studies with higher AUROC, sensitivity and specificity at the optimal cutoff levels. In addition, liver stiffness is included in our scores thus giving high accuracy as liver stiffness is an accurate and validated method for assessment of liver fibrosis in contrast to the previous scores that did not use it.

In comparison to the non invasive tests (APRI and FIB-4), cutoff values of the novel scores have higher AUROCs, sensitivity, specificity, accuracy, PPV and NPV.

In comparison to LSM by fibroscan, cutoff values of the novel scores have higher sensitivity while cutoff values of LSM by fibroscan have higher specificity. Thus, these novel scores are superior and more accurate than APRI and FIB-4 and can be used to improve the sensitivity of fibroscan for prediction of different stages of fibrosis.

5 | CONCLUSION

Combining AFP to serum biomarkers and liver stiffness measurement increases their diagnostic performance for prediction of different stages of liver fibrosis.

DISCLOSURE STATEMENT

All authors have no conflict of interest related to this manuscript.

ORCID

Mohammad El-Sayed http://orcid.org/0000-0003-3662-2509
Mai Mehrez http://orcid.org/0000-0002-7934-891X

REFERENCES

1. Kew M. Alpha-fetoprotein in primary liver cancer and other diseases. *Gut*. 1974;15:814–821.
2. Sakai M, Morinaga T, Urano Y, Watanabe K, Wegmann TG, Tamaoki T. The human alpha-fetoprotein gene. Sequence organization and the 5' flanking region. *J Biol Chem*. 1985;260:5055–5060.
3. Jin DK, Vacher J, Feuerman MH. α-Fetoprotein gene sequences mediating Afr2 regulation during liver regeneration. *Proc Natl Acad Sci USA*. 1998;95:8767–8772.
4. Adinolfi A, Adinolfi M, Lessof MH. Alpha-feto-protein during development and in disease. *J Med Genet*. 1975;12:138–151.
5. Halbrecht I, Klibanski C. Identification of a new normal embryonic haemoglobin. *Nature*. 1956;178:794–795.
6. Alpert ME, Uriel J, de Nechaud B. Alpha1 fetoglobulin in the diagnosis of human hepatoma. *N Engl J Med*. 1968;278:984–986.
7. Mehlman DJ, Bulkley BH, Wiernik PH. Serum alpha1-Fetoglobulin with gastric and prostatic carcinomas. *N Engl J Med*. 1971;285:1060–1061.

8. Mawas C, Kohen M, Lemerle J, Buffe D, Schweisguth O, Burtin P. Serum alpha-1 foeto-protein (fetuin) in children with malignant ovarian or testicular teratomas. Preliminary results. *Int J Cancer*. 1969;4:76–79.
9. Ishiguro T, Nishimura T. Radioimmunoassay of maternal serum—fetoprotein associated with pregnancy. *Am J Obstet Gynecol*. 1973; 116:27–33.
10. Dehghani–Firouzabadi R, Tayebi N, Ghasemi N, Tahmasbi Z. The association between second-trimester maternal serum alpha-fetoprotein in 14–22 weeks and adverse pregnancy outcome. *Acta Med Iran*. 2010;48:234–238.
11. Krantz DA, Hallahan TW, Sherwin JE. Screening for open neural tube defects. *Clin Lab Med*. 2010;30:721–725.
12. Duan Y, Li Y, Xue Q. Serological prenatal screening and diagnosis for Down syndrome. *Clin Exp Obstet Gynecol*. 2014;41:572–574.
13. AlSalloom AAM. An update of biochemical markers of hepatocellular carcinoma. *Int J Health Sci*. 2016;10:121–136.
14. Chen CH, Lin ST, Kuo CL, Nien CK. Clinical significance of elevated alpha-fetoprotein (AFP) in chronic hepatitis C without hepatocellular carcinoma. *Hepatogastroenterology*. 2008;55:1423–1427.
15. Babalı A, Cakal E, Purnak T, et al. Serum α-fetoprotein levels in liver steatosis. *Hepatol Int*. 2009;3:551–555.
16. Mousa N, Gad Y, Abdel-Aziz A, Abd-Elaal I. Increased α-Fetoprotein predicts steatosis among patients with chronic hepatitis C genotype 4. *Int J Hepatol*. 2012;2012:636392.
17. Kobeisy MA, Morsy KH, Galal M, Sayed SK, Ashmawy MM, Mohammad FM. Clinical significance of elevated alpha-foetoprotein (AFP) in patients with chronic hepatitis C without hepatocellular carcinoma in upper EGYPT. *Arab J Gastroenterol*. 2012;13:49–53.
18. Khairy M, Abdel-Rahman M, El-Raziky M, et al. Non-invasive prediction of hepatic fibrosis in patients with chronic HCV based on the routine pre-treatment workup. *Hepat Mon*. 2012;12:e6718.
19. Alboraie M, Khairy M, Elsharkawy A, et al. P0520: acceptability, reliability and applicability of liver biopsy and non-invasive methods for assessment of hepatic fibrosis and cirrhosis among hepatologists; a web based survey. *J Hepatol*. 2015;62:S510.
20. Wai CT, Greenson JK, Fontana RJ, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology*. 2003;38:518–526.
21. Sterling RK, Lissen E, Clumeck N, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. *Hepatology*. 2006;43:1317–1325.
22. Chou R, Wasson N. Blood tests to diagnose fibrosis or cirrhosis in patients with chronic hepatitis C virus infection: a systematic review. *Ann Intern Med*. 2013;158:807–820.
23. Geng XX, Huang RG, Lin JM, Jiang N, Yang XX. Transient elastography in clinical detection of liver cirrhosis: a systematic review and meta-analysis. *Saudi J Gastroenterol*. 2016;22:294–303.
24. Attallah AM, Omran MM, Farid K, et al. Development of a novel score for liver fibrosis staging and comparison with eight simple laboratory scores in large numbers of HCV-monoinfected patients. *Clin Chim Acta*. 2012;413:1725–1730.
25. Omran MM, Farid K, Emran TM, Attallah AA. Fibro-alpha score as a simple and useful non-invasive test for predicting significant liver fibrosis in chronic hepatitis C patients. *Arab J Gastroenterol*. 2011; 12:74–79.
26. Attallah AM, El-Far M, Omran MM, Farid K, Albannan MS, El-Dosoky I. Noninvasive diagnosis of liver fibrosis and cirrhosis in chronic hepatitis C patients. *J Clin Lab Anal*. 2013;27:121–129.
27. Castera L. Use of elastometry (FibroScan) for the non-invasive staging of liver fibrosis. *Gastroenterol Clin Biol*. 2007;31:524–530; quiz 500, 531–2. Review.
28. Hu KQ, Kyulo NL, Lim N, Elhazin B, Hillebrand DJ, Bock T. Clinical significance of elevated alpha-Fetoprotein (AFP) in patients with chronic hepatitis C, but not hepatocellular carcinoma. *Am J Gastroenterol*. 2004;99:860–865.
29. Attallah AM, Omran MM, Nasif WA, et al. Diagnostic performances of hepatitis C virus-NS4 antigen in patients with different liver pathologies. *Arch Med Res*. 2012;43:555–562.
30. Tai WC, Hu TH, Wang JH, et al. Clinical implications of alpha-fetoprotein in chronic hepatitis C. *J Formos Med Assoc*. 2009;108: 210–218.
31. Fung J, Lai CL, Fong DY, Yuen JC, Wong DK, Yuen MF. Correlation of liver biochemistry with liver stiffness in chronic hepatitis B and development of a predictive model for liver fibrosis. *Liver Int*. 2008;28:1408–1416.
32. Chen TM, Huang PT, Tsai MH, et al. Predictors of alpha-fetoprotein elevation in patients with chronic hepatitis C, but not hepatocellular carcinoma, and its normalization after pegylated interferon alfa 2a? ribavirin combination therapy. *J Gastroenterol Hepatol*. 2007;22:669–675.
33. Cedrone A, Covino M, Caturelli E, et al. Utility of alpha-fetoprotein (AFP) in the screening of patients with virus-related chronic liver disease: does different viral etiology influence AFP levels in HCC? A study in 350 western patients. *Hepatogastroenterology*. 2000;47: 1654–1658.
34. Wilfredo Canchis P, Gonzalez SA, Isabel Fiel M, et al. Hepatocyte proliferation in chronic hepatitis C: correlation with degree of liver disease and serum alpha-fetoprotein. *Liver Int*. 2004;24:198–203.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Gamil M, Alboraie M, El-Sayed M, et al. Novel scores combining AFP with non-invasive markers for prediction of liver fibrosis in chronic hepatitis C patients. *J Med Virol*. 2018;90:1080–1086. https://doi.org/10.1002/jmv.25026