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Cairo University fibrosis index (CUFI): A score based on microRNA for diagnosis of significant hepatic fibrosis: A biopsy based study

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***Abstract*---**Introduction: Identification of HCV- induced liver fibrosis is mandatory for tailoring therapy, and management of complications. The current study evaluated the accuracy of circulating miRNAs; in diagnosis of hepatic fibrosis. Patients and methods: Seventy HCV patients were subjected to routine laboratory investigations, HCV-RNA, serum miRNA-122, 221, 192, 224 , 375, and 885 by PCR, liver biopsy and calculation of the following scores: aspartate

aminotransferase (AST)/alanine aminotransferase (ALT) ratio (AAR), aspartate to platelet ratio index (APRI), FIB-4 score, Hui index, Fibrosis Index (FI), Fibro-Q , Fibro-Alfa Biotechnology Research Center (BRC) score and Gotebörg University Cirrhosis Index (GUCI). Results: Patients with significant and advanced fibrosis have significantly lower miR-122 (P < 0.0001 and P= 0.007, respectively). miR-122, bilirubin and miR-855 were found to be independent predictors of significant fibrosis in univariate analysis. A novel score; Cairo University Fibrosis Index (CUFI) based on microRNA 122, bilirubin and microRNA 855 were formulated for predicting significant liver fibrosis. The AUC of this score, for predicting significant and advanced hepatic fibrosis was 0.83 and 0.80 respectively. This AUC was higher than those of other fibrosis scores. Conclusion: Cairo University Fibrosis Index is better than the existing scores in assessing fibrosis in chronic HCV patients.

***Keywords*---**significant fibrosis, liver biopsy, microRNA.

Introduction

Hepatitis C virus (HCV) induced liver fibrosis is a dynamic, wound healing, process that results from ongoing damage to the hepatocytes from direct viral cytopathic effect or due to immunological response with subsequent activation of hepatic stellate cell and changes in extracellular matrix formation and degradation, including deposition of fibrillar collagen [1]. In the era of treatment of chronic HCV using highly efficient direct acting antivirals (DAAs), hepatic fibrosis staging as a triage for therapy indication is no longer as crucial as once believed [2-6]. Rather, precise identification of advanced hepatic fibrosis as well as cirrhosis is highly needed for tailoring HCV therapy, monitoring possible fibrosis regression after achieving sustained virological response and proper prevention and management of HCV related end stage liver disease complications [7-10]. Histopathology is the traditional gold standard method for determination of liver fibrosis stage, but needle liver biopsy procedure is invasive, and has some limitations including cost, risk of complications, sampling errors, inaccurate representation of unevenly distributed liver disease as the biopsy sample corresponds to a fraction of just $1/50{,}000^{th}$ of the entire liver [5].

Noninvasive methods for hepatic fibrosis staging in chronic HCV patients including physical (imaging techniques) and biological (serum biomarkers) have become increasingly available over the last few decades [7, 8, 10-14]. Micro RNAs (miRNAs) are small non-coding RNAs with an average length of 22 nucleotides that control translation and transcription of many genes [15]. MicroRNAs have an important role in the regulation of inflammatory diseases and are considered predictive biomarkers for liver diseases such as viral hepatitis, liver fibrosis and HCC [16, 17]. Few studies investigated the potential role circulating miRNAs in prediction of liver fibrosis stage.

The current study was conducted to evaluate the diagnostic accuracy of circulating microRNAs; miR-122, miR-192, miR-855, miR-375, miR-224, and

miR-221 in prediction of severity of hepatic fibrosis and to validate their usefulness against other commonly used noninvasive fibrosis biomarkers [Fibrosis Index (Fi), Fibro-Alfa , Hui index , aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio (AAR), Biotechnology Research Center (BRC) score, aspartate to platelet ratio index (APRI), Fibro-Q , Gotebörg University Cirrhosis Index) (GUCI) and fibrosis-4 (FIB-4) score using liver biopsy as gold stander.

Patients and Methods

In this cohort study, 70 consecutive patients with chronic HCV infection enrolled from Theodor Bilhariz research institute (TBRI). Eligible patients were 18 to 70 years of age with virological evidence of chronic HCV positivity by HCV antibodies and real-time polymerase chain reaction (RT-PCR). Exclusion criteria included patients with hepatitis B virus (HBV) co-infection, other causes of liver disease e.g. α1 anti-Trypsin deficiency, Wilson disease, haemochromatosis, alcoholic or non-alcoholic fatty liver disease and decompensated cirrhosis.

Clinical and Laboratory assessments

All included patients were subjected to detailed history taking, clinical examination and laboratory investigations including full blood count, liver biochemical profile (aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total and direct bilirubin, and serum albumin), international normalized ratio (INR) and HCV-RNA using reverse transcriptase-polymerase chain reaction (RT-PCR) (The Abbott Real Time HCV assay) with detection limit < 10 IU/mL. All testing was performed at a single reference laboratory.

miRNA extraction

Serum miRNA 122,192, 885, 375, 224 and 221 were evaluated by PCR (Sera had been stored at -80 C until use and RNA isolated from 500 mL serum using TriHReagentLS (Sigma-Aldrich, St. Louis, MO), chloroform and the mirVanaTM RNA isolation kit (Ambion-ABI, Austin, TX). Total RNA was eluted in 100 mL and stored at -20C. Five mL of RNA reverse transcribed with the TaqManH miRNA reverse transcription kit and the TaqManH miRNA assay specific RT primers for miRNAs 122,192,885,375,224 and 221 according to the instructions of the manufacturer (ABI). Real-time PCR was performed with three mL of each cDNA on a StepOneTMPlus Real-Time PCR System (ABI) in duplicates.

Liver biopsy

Ultrasound guided needle liver biopsy was performed to all included patients by single expert hepatologist who was blinded to patients clinical data using disposable automatic Guillotine tru-cut needle (16-gauge). Acceptable sample was at least 10 mm in length and containing at least 5 complete portal tracts. Biopsy specimens were stained with hematoxylin-eosin and silver. Fibrosis stage was determined according to the METAVIR group scoring system [18].

Noninvasive assessment of hepatic fibrosis

For all included patients all the following scores were calculated according to corresponding equation: Fibrosis Index (Fi): 8 – (0.01 × platelets (10^9/L)) - albumin (g/dL)[19]. Fibro-Alfa: 1.35 + AFP (IU/ml) × 0.009584 + AAR (AST/ALT) × 0.243 –platelet count (109/l) × 0.001624.[20]. Hui index: 3.148 + 0.167 x BMI + 0.088 x bilirubin - 0.151 x albumin - 0.019 x platelet. [21]. Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio (AAR): AST/ALT [22]. Biotechnology Research Center (BRC) score: 1.02 + 0.4 × AFP (U/l) + 0.19 ×Age (years) − 0.02 × Platelet count (10^9/l) [23]. Aspartate to platelet ratio index (APRI): (AST (IU/L) /upper limit of normal/platelet count (10^9/L) × 100 [24]. Fibro-Q: 1.35 + AFP (IU/ml) × 0.009584 + AAR (AST/ALT) × 0.243 –platelet count (10^9/l) × 0.001624. [25]. Gotebörg University Cirrhosis Index) (GUCI): AST× INR ×100 / Platelet count (10^9/L) [26]. Fibrosis-4 (FIB-4) score: [Age [yrs.] × AST [U/L] / (platelet count [109/L] × (ALT [U/L] 1/2)] [27]

Ethical approval

This study was approved by ethics committee of Endemic Medicine and Hepatology Department, faculty of Medicine, Cairo University, Egypt .The current study was conducted in accordance with the Declaration of Helsinki 1973 and Good Clinical Practice guidelines. Ethics Committee of Endemic Medicine and Hepato-gastroenterology Department reviewed and approved the protocol, and all patients gave written informed consent before participation in the study.

Statistical analysis

Results were statistically analyzed using SPSS software package version 15.0 (SPSS Inc., Chicago, IL). Numerical data were expressed as mean ± SD and differences were performed using analysis of variance (ANOVA) or Student's t-test. Tests were significant when the P-value < 0.05. Patients were classified into significant liver fibrosis (F2–F4) and advanced liver fibrosis (F3–F4). To assess the ability of each biomarker for differentiating between the two groups, the area under the receiver operating characteristics (AUROC) curves were plotted; significant biomarkers were selected and entered in stepwise linear regression analysis to develop a score that combined the independent factors for identifying significant fibrosis. The best cutoff value of the predictive score was optimized for identifying significant fibrosis. On the other hand, the diagnostic performances of our developed score was compared with others common noninvasive liver fibrosis scores. $p>0.05$ is considered non-significant; $p<0.05$ is considered significant. p value < 0.01 is considered highly significant, $p < 0.001$ is considered very significant and $p < 0.0001$ is considered extremely significant

Results

The study cohort included 70 chronic HCV patients [mean age 40.9± 8.5 years, 70% men (n=49)]. According to liver histopathology, F0, F1, F2, F3, F4 was identified in 7, 37, 14, 11, and 1 patient respectively. Baseline demographic and laboratory values and mi-RNAs level are shown in table (1) The baseline data and the mean values of candidate miRNAs were compared between patients with non-

significant hepatic fibrosis (F0-F1) and those with significant (F2 - F4) and advanced hepatic fibrosis (F3–F4). miRNA 122 was statistically significantly lower in patients with significant hepatic fibrosis (F2 - F4) and in those with advanced hepatic fibrosis (F3–F4). ($P < 0.0001$ and $P= 0.007$, respectively). (Table 2)

Univariate analysis of all comparing biomarkers in the present study identified micro RNA 122, bilirubin and micro RNA 855 as independent markers for discriminating significant liver fibrosis. The AUC were 0.78, 0.67and 0.63, respectively (Table 3, figure 1 A - C). The previous analysis indicated that micro RNA 122 was the most efficient index among other biomarkers. (Table 3) The multivariate discriminant analysis (MDA) selected the best overall formula combining microRNA 122, bilirubin and microRNA 855 as a novel noninvasive score for predicting significant liver fibrosis. Cairo University Fibrosis Index (CUFI) = 4.558 – (micro RNA 122 x 0.089+ micro RNA 855 x 0.051+ bilirubin x 0.366), where 4.558 is a numeric constant. The AUC of this score was assessed for identifying significant fibrosis showing an AUC of 0.83 (figure 1D). A cut-off value of 0.41 had 77% sensitivity, 75% specificity, 65% positive predictive value, 85 % negative predictive value and efficiency of 76% for predicting significant liver fibrosis (Table 4)

The mean ± SD, areas under the ROC curves of the predictive score and common noninvasive liver fibrosis scores were summarized in table 5. The AUC of common liver fibrosis scores; FI, Fibro- Alfa, Hui index, AAR, BRC, APRI, Fibro-Q, GUCI and FIB 4 were 0.46, 0.53, 0.54, 0.60, 0.61, 0.62, 0.62, 0.62 and 0.67; respectively for predicting significant fibrosis. Our predictive score yielded an AUC of 0.83 for predicting significant fibrosis and 0.80 for predicting advanced fibrosis which was the greatest among common liver fibrosis scores. (Table 5)

Table 1: The baseline data of chronic HCV infected patients at different fibrosis stages

Variable	F0 (n=7)	F1 (n=37)	F2 (n= 14)	F3 (n= 11)	P value
Age (years)	42.29 ± 13.39	38.08 ± 8.27	43.36 ± 5.37	45.82 ± 5.47	0.024
ALT (U/L)	40.71 ± 12.63	38.43 ± 12.16	38.21 ± 13.56	41.09 ± 14.77	0.793
AST(U/L)	32.29 ± 8.01	37.54 ± 11.04	40.57 ± 8.71	42.45 ± 12.32	0.258
Bilirubin (mg/dl)	0.80 ± 0.08	0.78 ± 0.20	0.71 ± 0.14	0.73 ± 0.26	0.415
Albumin (g/L)	43.71 ± 3.55	42.13 ± 3.28	42.43 ± 3.89	43.64 ± 4.03	0.680
Hb (g/dl)	12.88 ± 1.02	13.75±1.34	13.80 ± 1.49	13.70 ± 1.08	0.581
PLT ($\times 10^9$/L)	260.57 ± 73.26	283.08 ± 76.57	273.57 ± 88.11	295.09 ± 96.21	0.830
PC (%)	89.14 ± 5.11	86.43 ± 7.57	85.71 ± 5.57	85.55 ± 6.68	0.568
INR	1.10 ± 0.06	1.14 ± 0.09	1.14 ± 0.06	1.15 ± 0.07	0.533
Glucose (mg/dl)	91.86 ± 8.91	92.73 ± 14.22	91.79 ± 14.0	90.82 ± 13.20	0.757
PCR (IU ml X10 ^{4})	47,33 ± 28,1	109,77 ± 149,58	123,9 ± 161,79	61,39 ± 104,23	0.627
AFP (U/L)	5.46 ± 3.91	5.56 ± 3.02	5.45 ± 3.35	5.47 ± 2.82	0.110
Micro RNA 122	30.75 ± 1.40	29.42 ± 2.43	27.37 ± 2.60	27.08 ± 1.85	0.001
Micro RNA 192	26.91 ± 1.89	27.06 ± 1.72	27.61 ± 1.46	26.93 ± 2.04	0.839
Micro RNA 855	25.73 ± 2.45	26.59 ± 1.9	25.86 ± 1.75	25.55 ± 1.10	0.400
Micro RNA 375	29.83 ± 3.74	29.67 ± 3.87	30.84 ± 2.90	29.99 ± 3.69	0.628
Micro RNA 224	29.81 ± 3.20	32.08 ± 2.95	29.77 ± 2.72	31.60 ± 4.11	0.125
Micro RNA 221	34.91 ± 1.82	34.19 ± 6.47	34.81 ± 4.28	33.17 ± 3.46	0.841

Continuous variables were expressed as mean ± SD.

Table 2: Comparison between non-significant hepatic fibrosis (F0-F1) and those with significant (F2 - F4) and advanced hepatic fibrosis (F3–F4)

Variable	Non significant fibrosis (n= 44)	Significant fibrosis (n= 26)	P value	Non advanced fibrosis (n= 58)	Advanced fibrosis (n= 12)	P value
Age (years)	38.75 ± 9.21	44.73 ± 5.54	0.004	39.86 ± 8.63	46.3 ± 5.5	0.015
ALT (U/L)	38.80 ± 12.11	40.00 ± 13.85	0.704	38.6± 12.36	42.08 ± 14.49	0.399
AST(U/L)	36.70 ± 10.72	41.62 ± 10.11	0.063	37.64 ± 10.33	42.83 ± 11.82	0.126
Bilirubin (mg/dl)	0.79 ± 0.19	0.71 ± 0.19	0.102	.7667 ± .178	0.71 ± 0.25	0.345
Albumin (g/L)	42.39 ± 3.34	42.92 ± 3.85	0.541	42.39 ± 3.44	43.50 ± 3.87	0.326
Hb (g/dl)	13.61 ± 1.32	13.78 ± 1.27	0.618	13.66 ± 1.35	13.73 ± 1.04	0.857
PLT ($\times 10^9$/L)	279.50 ± 75.67	280.54 ± 89.54	0.959	278.1± 78.1	288.67 ± 94.40	0.681
PC (%)	86.86 ± 7.25	86.00 ± 6.11	0.612	86.59 ± 6.86	86.33 ± 6.93	0.908
INR	1.13 ± 0.08	1.14 ± 0.07	0.742	1.14 ± 0.08	1.14 ± .07	0.890
Glucose (mg/dl)	92.59 ± 13.43	92.08 ± 13.61	0.878	92.39 ± 13.45	92.42 ± 13.74	0.996
PCR (IU ml X10 ^{4})	99,84 ± 139,19	94,26 ± 138,0	0.871	105,66 ± 143,86	59,61 ± 99,57	0.295
AFP (U/L)	5.54 ± 3.13	5.80 ± 3.48	0.747	5.52 ± 3.15	6.22 ± 3.72	0.502
Micro RNA 122	29.63 ± 2.33	27.15 ± 2.26	< 0.0001	29.09 ± 2.57	26.90 ± 1.87	0.007
Micro RNA 192	27.03 ± 1.73	27.32 ± 1.70	0.509	27.17 ± 1.67	26.98 ± 1.95	0.718
Micro RNA 855	26.46± 1.99	25.76 ± 1.46	0.126	26.31 ± 1.94	25.65 ± 1.09	0.258
Micro RNA 375	29.69 ± 3.81	30.27 ± 3.32	0.523	29.98 ± 3.62	29.61 ± 3.77	0.752
Micro RNA 224	31.72 ± 3.07	30.65 ± 3.41	0.185	31.25 ± 3.08	31.69 ± 3.93	0.663
Micro RNA 221	34.30 ± 5.96	33.94 ± 3.99	0.786	34.43 ± 5.57	32.84 ± 3.46	0.336

Table 3: Area under ROC of different variable for detection of significant fibrosis

Variable	Std. Error	P value	AUC	95% CI
Micro RNA 122	0.055	< 0.0001	0.78	0.686-0.900
Bilirubin	0.068	0.017	0.67	0.538-0.806
Micro RNA 855	0.067	0.048	0.63	0.486-0.750
Score	0.049	< 0.0001	0.83	0.73- 0.93

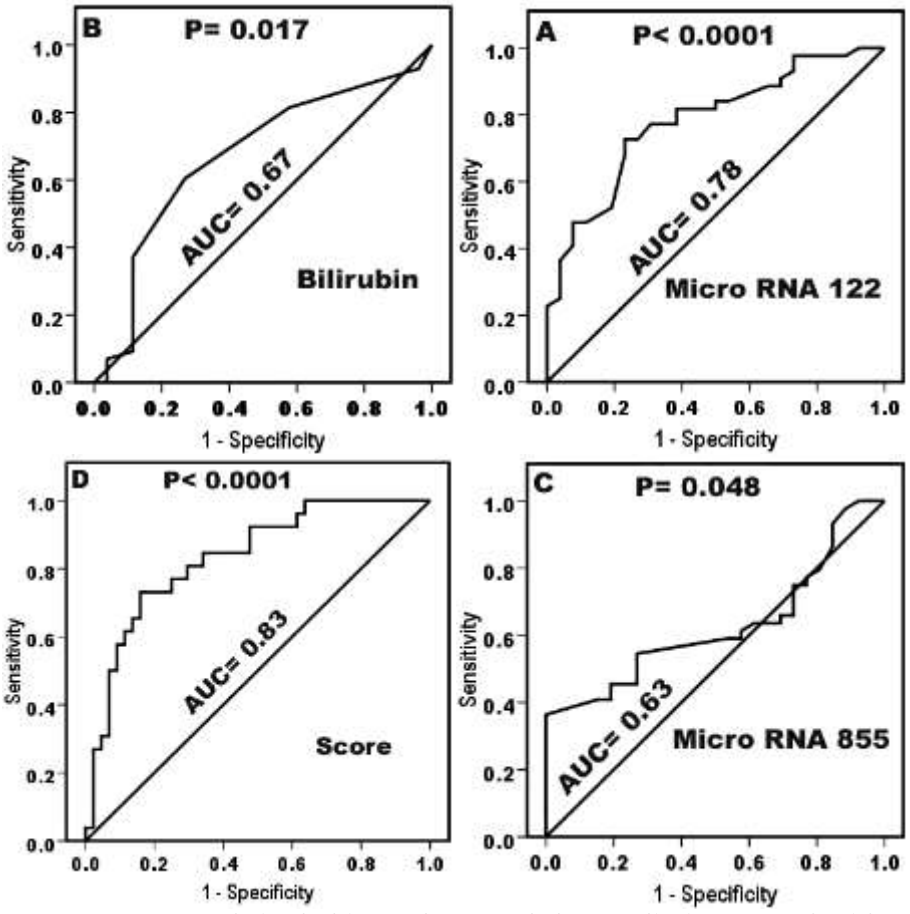

Figure 1: ROC curves of single biomarkers and the predictive score for identifying significant fibrosis

Table 4: Sensitivity, Specificity, Positive predictive value of CUFI score for predicting significant liver fibrosis

Score cutoffs	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Efficiency
0.38	84.6	63.6	57.9	87.5	71.4
0.4	80.8	68.2	60	85.7	72.9
0.41	76.9	75	64.5	84.6	75.7
0.42	73.1	79.5	67.9	83.3	77.1

Table 5.Comparison of our predictive score and common liver fibrosis scores for predicting significant and advanced fibrosis

Variable	Non significant fibrosis (n= 44)	Significant fibrosis (n= 26)	P value	AUC	Non advanced fibrosis (n= 58)	Advanced fibrosis (n= 12)	P value	AUC
FI	-37.18 ± 3.45	-37.73 ± 3.93	0.545	0.46	-37.18 ± 3.53	-38.39 ± 4.03	0.295	0.399

Fibro-Alfa	1.19 ± 0.14	1.22 ± 0.19	0.434	0.53	1.20 ± 0.16	1.19 ± 0.17	0.937	0.485
Hui score	-4.10 ± 0.26	-3.89 ± 2.17	0.956	0.54	-4.06 ± 1.81	-3.86 ± 2.29	0.740	0.561
AAR	0.99 ± 0.33	1.12 ± 0.38	0.151	0.60	1.04 ± 0.37	1.07 ± 0.27	0.812	0.569
BRC	5.0 ± 2.67	6.23 ± 2.99	0.082	0.61	16.61 ± 6.55	17.99 ± 5.76	0.500	0.579
APRI	0.35 ± 0.15	0.40 ± 0.13	0.180	0.62	0.37 ± 0.15	0.39 ± 0.12	0.546	0.580
Fibro -Q	1.68 ± 0.83	2.37 ± 1.53	0.018	0.62	1.87 ± 1.11	2.25 ± 1.47	0.308	0.583
GUCI	16.01 ± 6.56	18.25 ± 5.99	0.159	0.62	5.24 ± 2.69	6.54 ± 3.39	0.151	0.602
FIB -4	0.90 ± 0.44	1.21 ± 0.59	0.015	0.67	0.98 ± 0.51	1.18 ± 0.50	0.227	0.632
score	0.28 ± 0.23	0.57 ± 0.21	< 0.0001	0.83	0.35 ± 0.25	0.60 ± 0.18	0.002	0.800

Discussion

Liver disease is a major cause of mortality and morbidity in HCV infected patients [5, 28]. Accurate determination of disease stage is mandatory for clinical decision making. Still liver biopsy is considered the gold standard for diagnosis of liver fibrosis [29]. However, its invasiveness, the potential associated complications and poor sample quality urge the search for noninvasive diagnostic markers for liver fibrosis [30]. The need to find predictors of hepatic fibrosis stage at the molecular level is increasing as hepatic fibrosis progression may result in hepatocellular carcinoma development [31, 32]. The miRNAs are now considered to be important indicators of liver fibrosis [33], and liver carcinogenesis [32].

In the current study, we evaluated the performance of microRNAs as hepatic fibrosis biomarkers. miR-122 was significantly lower in patients with significant and advanced fibrosis ($P < 0.0001$ and $P= 0.007$, respectively). Our study showed more decrease in serum miR-122 in patients with advanced hepatic fibrosis (F3,4) when compared with significant fibrosis (F2-4) which agreed with Trebicka et al who stated that loss of functional hepatocytes in the late stages of fibrosis (F3–4) might cause decreased serum levels of miRNA-122 [34]. Moreover, the suppressive function of miR-122 that hinders the proliferation of hepatic stellate cells and fibrogenesis is absent in late stages of fibrosis. [35]. Also, many studies proved a negative correlation between miR-122 and fibrosis stage in chronic HCV infection, HCV-based HCC, and cirrhosis [36, 37]

Furthermore, we formulated a novel score (CUFI) which shows greater diagnostic value for diagnosing significant and advanced hepatic fibrosis taking liver biopsy as the gold standard (AUR 0.83, 0.8 respectively) . The score included microRNA 122, microRNA 855 and bilirubin. It is well known that changes in miRNA-122 serum levels occurs early in liver disease , suggesting that that miRNA -122 can be a reliable predictor of hepatic injury [33]. Additionally, miR-122 induces HCV translation, and stimulates viral genomic RNA replication [38]. Also, it is is negatively correlated with fibrosis in HCV-infected patients [36, 37]. miR-885 was found to correlate with different liver pathologies [39-41]. Bilirubin is the lipophilic end product of heme breakdown [42]. Hyperbilirubinemia is a common in chronic liver disease and serum bilirubin is routinely included in biochemical assessment of such patients, Serial measurement of serum bilirubin is might be indicative of liver disease progression being an indirect marker of hepatic fibrosis [43]

Our novel score CUFI which is composed of serum bilirubin, miRNA -122 and miRNA -855 performed even better than common liver fibrosis scores. It yielded AUC 0.83 for predicting significant fibrosis and 0.80 for predicting advanced fibrosis which was the greatest score among common liver fibrosis scores. On comparing CUFI and common noninvasive liver fibrosis scores for predicting significant and advanced liver fibrosis, It was found that the AUC of common liver fibrosis scores; FI, Fibro- Alfa, Hui index, AAR, BRC, APRI, Fibro-Q, GUCI and FIB 4 were 0.46, 0.53, 0.54, 0.60, 0.61, 0.62, 0.62, 0.62 and 0.67; respectively for predicting significant fibrosis. While it was 0.40,0.49, 0.56, 0.57, 0.58, 0.58, 0.58, 0.60, 0.63 for predicting advanced fibrosis. This could be explained by the fact that most of the common liver fibrosis scores depend on multiple biochemical and serum parameters (e.g. AST, ALT, AFP), which may vary with many factors such as blood drawing time, sample delivery time and liver functional status [44]. On the other hand, miRNAs are stably present in the blood, making them suitable as biomarkers [45].

Conclusion

Cairo University Fibrosis Index is better than the existing scores in assessing fibrosis in chronic HCV patients.

Limitation of our study included small sample, so our results should be validated on a larger sample

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Abbreviations: FI= fibrosis index; AAR= aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio; APRI= aspartate to platelet ratio index; BRC = Biotechnology Research Center; GUCI= Gotebörg University Cirrhosis Index.

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