Original Article

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Value of hepatic artery resistive index in evaluation of liver fibrosis related to non-alcoholic fatty liver diseases

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Abstract

Background: Staging of liver fibrosis is essential for managing patients with nonalcoholic fatty liver disease (NAFLD). Liver biopsy has well-known limitations and cannot be proposed to all patients. Previous studies have demonstrated that hepatic artery resistive index (HARI) is significantly altered in NAFLD patients. The aim of this study is to assess the value of (HARI) in evaluating the progression of liver fibrosis in NAFLD patients.

Patients and methods: This study was carried out on 100 NAFLD patients. All patients had undergone Doppler ultrasound and transient elastography (TE) with controlled attenuation parameter (CAP) to quantify the degree of steatosis. Laboratory work and calculation of FIB-4, AST-platelets ratio index (APRI), NAFLD fibrosis score (NFS) were done. Sensitivity and specificity of HARI values for predication of liver fibrosis were estimated by the receiver operating characteristic curve. **Results:** The study revealed a statistically significant positive correlation of HARI with liver stiffness measurement (LSM) measured by fibroscan, FIB4, NFS, age, Hba1c, fasting blood sugar (P <0.0001 for all) and LDL, HDL and albumin. However, a significant negative correlation of HARI with CAP was detected (P= 0.03). At a cutoff value of 0.76, HARI had 80% sensitivity and 76% specificity for prediction of advanced fibrosis (> 9.1 KPa) with area under ROC curve equal to 0.826. Moreover, HARI at a cutoff value 0.74 showed 83% sensitivity and 72% specificity for the prediction of liver cirrhosis (≥ 10.4 KPa) with the area under the ROC curve equal to 0.803. **Conclusion:** HARI is a good non-invasive tool to predict the risk of liver fibrosis progression in patients with NAFLD particularly advanced fibrosis and cirrhosis. HADRI correlates with other non-invasive methods of assessment of fibrosis including LSM, CAP, FIB4 and NFS, and may provide an easy, available tool for monitoring of patients with NAFLD.

Introduction

NAFLD is a clinical syndrome characterized by liver macrovesicularsteatosis. The determination of the stage of fibrosis is a common clinical concern in patients with NAFLD. Unfortunately, due to well-known limitations (invasiveness and sampling variability), liver biopsy cannot be recommended for all patients, particularly with high prevalence of NAFLD worldwide [1].

Noninvasive strategies for evaluating NAFLD depend on measuring serum biomarker levels or using imaging techniques such as conventional ultrasonography (US). A computerized tomography, Magnetic resonance imaging (MRI), and US- based elastography to measure liver stiffness [2].

US examinations are a simple, non-invasive, and widely available tool for following up the health of the liver parenchyma. Furthermore, unlike invasive biopsy sampling, it allows the examiner to gather data on functional changes in the liver induced by steatosis, like hepatic vessel flow [3].

Transient Elastography (TE) has become the most important tool in the non- invasive staging of liver disease [4-6]. However, TE has some limitations, including variability due to the probe position/inclination, respiratory movements, narrow intercostal spaces or ascites, and a shortage of well-defined vendor-specific variability. TE also obliges specific training which is not always available, is imprecise in stage 2,3 of fibrosis, and its values are affected by inflammation, BMI, steatosis, and cholestasis [7-9]. On the contrary, A HARI measurement may be used with a standard procedure and parameters, which may decrease variability among patients [10].

Former research has shown that (HARI) decreases as the grade of hepatic steatosis increases [3,11-13], and tends to increase in cirrhotic patients [14], However, there is no evidence of a possible correlation between HARI and the severity of fibrosis in NAFLD patients. As a result, the purpose of this study was to look into a possible relationship between the hepatic arterial resistive index and the stage of liver fibrosis associated with NAFLD, as well as compare it to the TE and other clinical and biochemical.

Patients and methods

This study was carried out on 100 patients (28 males and 72 females) with NAFLD aged between (30-66) years old recruited from an out and inpatient clinic of Tropical medicine department, Mansoura University, Dakahlya, Egypt, between June 2018 and May 2021. All patients aged 18 years old and above with body mass index (BMI) more than 25 and evidence of any grade of fatty liver by ultrasonography. All subjects have signed a written

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informed consent before enrollment in the study. An approval was provided by the Institutional Review Board (IRB) of the faculty of medicine-Mansoura University (MD.18.8.79). All subjects had undergone detailed history taking in addition to clinical assessment.

Patients were excluded if they have any of the following; alcohol consumption, viral hepatitis e.g. (HBV, HCV), autoimmune hepatitis, wilson's disease, hemochromatosis, steatogenic drugs, hepatic or extrahepatic malignancy, vascular liver diseases (Budd-Chiari syndrome, sinusoidal obstruction syndrome).

Anthropometric measures: BMI was calculated according to the following equation: BMI = Weight (Kg) / Height (m2). Waist circumference was measured using a measuring tap placed in a horizontal plane around the abdomen at the level of the iliac crest. The measurement was made at the end of expiration.

Laboratory work: Liver function tests (ALT, AST, serum albumin, serum bilirubin, prothrombin time), creatinine, complete blood count, virology (HBS Ag, HCV Ab), fasting and 2hrs pp blood sugar, Hba1c, serum cholesterol, TGs, LDL, HDL, serum uric acid, autoimmune markers (ANA, ASMA), AFP, were evaluated.

Radiology Work: All patients had undergone pelvic–abdominal ultrasound as a screening tool, Doppler on the hepatic artery to measure hepatic artery resistive index and transient elastography to determine degree of steatosis& fibrosis.

Ultrasound and Doppler: All patients fasted overnight or for more than 6 hours before the sonography examination, which was performed with a multifrequency (2–5 MHz) convex transducer by a single experienced sonologist who was blinded to the patients' transient elastography results. The following data was gathered; the size of the liver and spleen, as well as the grade of echogenicity (longitudinal diameter of the right lobe of the liver). HARI Doppler ultrasound evaluations were performed after the patients had been lying in the supine or left posterior oblique position for 15 minutes during deep inspiration. First, the main hepatic artery peak velocity (Vmax) was measured in metres per second at the portahepatis with a Doppler angle ranging from 45° to 60° . Second, using the following equation, the hepatic artery RI value was calculated automatically from the Doppler trace: RI = (peak systolic velocity – end-diastolic velocity / peak systolic velocity). The following information was acquired: echogenicity and size of liver and spleen (longitudinal diameter of the right lobe of the liver)

Transient Elastography: TE using FibroScan® was performed by an experienced herpetologist using an XL probe, on patients who fasted for at least 6 hours prior to examination, in the supine position, with the right arm in full abduction, on the mid-axillary line with the probe tip placed in the 9thto 11th intercostal space with a minimum of 10 measurements [15]. Liver stiffness (LS) values were regarded as valid if the following criteria were met; number of valid measurements is at least 10. A success rate above 60%. An interquartile range (IQR, reflecting the variability of measurements) is less than 30% of the median LS measurements (M) value (IQR/M ≥30%), [15]. The XL probe was used in this study due to the presence of morbidly obese patients. The measured depth was between 35 and 75 mm. Controlled attenuation parameter (CAP) was also obtained to quantify the degree of steatosis. According to the manufacturer's instructions, in addition to previous studies, the stages of fibrosis (F0: 1–6, F1: 6.1–7, F2: 7–9, F3: 9.1–10.3, and F4: ≥ 10.4) were defined in kPa [16,17]. Moreover, steatosis stages (S0: < 215, S1: 216–252, S2: 253–296, S3: > 296) were defined at dB/m [18].

Non-invasive scores for assessment of liver fibrosis: Non-invasive scores for the assessment of liver fibrosis (APRI, FIB-4, NAFLD fibrosis score) were calculated using standard formulas.

1). NAFLD Fibrosis Score = -1.675 + 0.037 × Age (years) + 0.094 × BMI (kg/m2) + 1.13 × IFG/diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio – 0.013 × Platelet (×109/L) – 0.66 × Albumin (g/dL) The NAFLD fibrosis score (NFS) was used to separate NAFLD patients with and without advanced liver fibrosis. We used the NFS score to classify the probability of fibrosis as < -1.45 for low probability, > -1.45 to < 0.67 for intermediate probability, and > 0.67 for high probability [19].

2). FIB-4 Score = (Age x AST) / (Platelets x √ (ALT)) [20,21].

3). APRI = [AST/AST (ULN)] /platelet (109/L) [20,22].

Statistical analysis

Analysis of data was done using SPSS (Statistical package for social science) program version 25.0. Statistical analysis of the data was done by using Statistical Package for Social Science (SPSS) version 25.0. The normality of the distribution was checked by Kolmogrov Smirnov test to determine parametric or nonparametric distribution. Quantitative data were expressed as Mean± SD for parametric data and as median and range for non-parametric data while qualitative data were expressed as frequency and percent. The significance of difference was analysed by the Kruskal Wallis test & then Mann-Whitney test for multiple comparisons. Categorical variables were compared using the likelihood-ratio v 2 test or Fisher' s exact test. A Spearman's correlation analysis was performed to evaluate the correlation between HARI values and other variables included in this study. Significance was considered when P value ≤ 0.05. ROC curve analysis was done to detect cutoff values of HARI that have higher sensitivity and specificity for the prediction of stage of liver fibrosis.

Results

Table 1 shows descriptive data of demographic, anthropometric, biochemical parameters and noninvasive methods for assessment of liver fibrosis and steatosis.

Table 2 shows the correlation of HARI with demographic, anthropometric and biochemical parameters of study patients. There was a statistically significant positive correlation of HARI with age (P <0.0001), FBS (P <0.0001), Hba1c (P= 0.001), low density lipoprotein (P=

0.01), high density lipoprotein (P= 0.05) and albumin ((P= 0.05) while no statistically significant correlation of HARI with other biochemical parameters was detected.

Table 3 shows the correlation of HARI with noninvasive methods for assessment of fibrosis and steatosis. There was a statistically significant positive correlation of HARI with liver stiffness measurement, NFS and FIB4 (P <0.0001) and a statistically significant negative correlation of HARI with CAP (P= 0.03). No correlation was found between HARI and APRI (p= 0.195).

Table 4 shows a comparison of noninvasive methods for assessment of fibrosis between the F0 group, mild fibrosis (F1-2) and advanced fibrosis/cirrhosis (F3-4) group according to liver stiffness measurement. As regards CAP, compared to F0, F1-F2 showed a non-significant increase in CAP (p=0.6) while F3-F4 showed a significant decrease (p=0.003). Furthermore, a significant decrease was found when compared F1-F2 versus F3-F4 (p =0.005). As regards HARI, compared to F0, F1-F2 showed a non-significant increase in HARI (p=0.1) while F3-F4 showed a significant increase (p=0.001). Furthermore, a significant increase was found when comparing F1-F2 versus F3-F4 (p =0.002). As regards FIB4, compared to F0, F1-F2 and F3-F4 showed significant increases in FIB4 (p=< 0.0001) while a non-significant increase was found when comparing F1-F2 versus F3-F4 (p = 0.4). As regards the APRI, compared to F0, F1-F2 and F3-F4 showed significant increase in FIB4 (p=< 0.02) while a non-significant increase was found when comparing F1-F2 versus F3-F4 (p = 0.1). As regards NFS, compared to F0, F1-F2 and F3-F4 showed significant increases in NFS (p=< 0.0001 and 0.01 respectively), while a non-significant increase was found when comparing F1-F2 versus F3-F4 (p = 0.3). Figure (1) a Table (5) shows that at cutoff point 0.67, sensitivity and specificity of HARI for prediction of early fibrosis (> 6.1 and < 9.1 KPa) was 69% and 57% respectively with an area under the curve (0.611). Figure (1) b, Table (5) shows that at cutoff point 0.76, sensitivity and specificity of HARI for prediction of advanced fibrosis (> 9.1 KPa) was 80% and 76% respectively with an area under the curve (0.826). Figure (1) c, Table (5) shows that at cutoff point 0.74, sensitivity and specificity of HARI for prediction of cirrhosis (≥10.4 KPa) was 83% and 72% respectively with an area under the curve (0.803).

Discussion

In the present study, there was a statistically significant positive correlation of HARI with FIB4, NFS and LSM. In line with our findings, Ergelen et al. Demonstrated correlation of HARI values with LSM values [10]. In addition, Tana et al. establish a significant positive correlation between HARI and NFS. They found that in patients with NFS > 0.675, HARI exceeded the range of controls, implying that fibrous tissue depositions may induce arterial rigidity to increase [13]. Furthermore, studies have shown that HARI is a significant predictor of fibrosis and cirrhosis due to different etiologies e.g. Viral hepatitis [23,24], alcoholic liver diseases [25], liver transplantation [26], liver cirrhosis with or without portal vein thrombosis [27]. On the contrary, Alempijevic et al. found that HARI has no significant correlation with significant liver fibrosis and cirrhosis. This discrepancy may be due to the small sample size and presence of various etiologies in that study, unlike homogeneity in the etiologies of other studies [28].

On the other hand, HARI showed a statistically significant negative correlation with CAP. These results agree with several studies [3,11-13], that found a negative correlation of HARI with steatosis degree. Mihmanli et al. Assume that the portal vein branch is more compressed by fat accumulation than the hepatic arterial branch. This causes a decrease in portal system blood flow volume and a compensatory increase in hepatic arterial system blood supply, which may be accomplished by increasing the end diastolic velocity of the hepatic artery, as reflected by a decrease in hepatic arterial resistive index [11].

Based on classification of patients in the present study according to LSM values, HARI showed a significant difference only when comparing (F0 versus F3-4) and (F1-2 versus F3-4). However a non-significant difference was detected when comparing (F0 versus F1-2) indicating that it may have better sensitivity for detection of advanced fibrosis. Additionally, when comparing (F0, F1-2, F3-4) groups, there was a significant increase in non invasive parameters for assessment of liver fibrosis including FIB4, NFS, APRI, LSM.

The present study revealed no correlation between transaminase level and HARI, a finding reported in a previous study by Ergelen et al.,[10]. Piscaglia et al. Found no link between HARI values and hepatic histological changes, e.g., degeneration, inflammation, and necrosis [23]. Thus, HARI evaluation may also be more precise for detecting significant fibrosis in patients with higher liver enzyme levels, a well-known limitation of TE [29]. Koch and Sumbul reported that although liver fibrosis (LF) occurred more frequently in those with elevated transaminases, no independent association was detected [30].

In our study, there is an essential correlation of HARI with age which is compatible with the results of earlier studies [31-33]. We also observed a significant correlation of HARI with Hba1c consisting with Koch and sumbul who found that each 1% increment in HbA1c level was associated with 36.7% increased likelihood of liver fibrosis [30]. Supporting our results, Hizli et al. Reported that, obese subjects with NAFLD and insulin resistance (IR) had significantly higher HARI compared to obese subjects with NAFLD but without IR. They suggest that HARI might be used as a simple and non-invasive screening method to predict IR in obese children with NAFLD [32].

Regarding the lipid profile in our study, we detected a correlation of HARI with LDL. Méndez-Sánchez et al. Also showed that steatohepatitis and liver fibrosis have higher VLDL and LDL serum concentration than simple steatosis [34]. As a possible explanation, Charlton et al. Reported that NASH is associated with a highly altered hepatic synthesis of apoB100, compared with obese (BMI-matched) persons without NASH [35].

Table 1. Demographic, anthropometric, biochemical parameters and noninvasive methods for assessment of fibrosis and steatosis in studied patients.

Parameter	Mean ± SD /Median (range) /Frequency (%)
Age (years)	47 ± 8.7
Sex: male / female	28 (28%)/ 72 (72%)
BMI (Kg/m2)	35.4 ± 4.9
Waist circumference (centimeters)	113 ± 11
FBS (mg/dl)	95 (75 – 366)
Hba1c (%)	6.3 ± 1.3
Cholesterol (mg/dl)	228 ± 49
Triglyceride (mg/dl)	161.6 ± 54
Low density lipoprotein; (mg/dl)	154.6 ± 43
High density lipoprotein; (mg/dl)	46 ± 8
AST (U/L)	35 (18 – 160)
ALT (U/L)	32 (17 – 153)
Albumin (g/dL)	4.2 ± 0.3
Bilirubin (mg/dl)	0.8 ± 0.2
INR	1.05 ± 0.1
S. Creatinine (mg/dl)	0.9 ± 0.3
S. Uric acid (mg/dl)	5.4 ± 1.1
White blood cells (×103/µL)	6.2 ± 1.8
Hemoglobin	12.3 ± 1.4
Platelets (×103/µL)	250 ± 59
FIB4	1.18 (0.55 – 7.5)
APRI	0.36 (0.16 – 3.02)
NAFLD fibrosis score	-1.43 (-3.48 – 2.11)
HARI	0.69 ± 0.1
LSM (kPa)	5.5 (3.1- 18)
CAP (dB/m)	309 ± 52

BMI, body mass index; **2hpp,** 2 hour postprandial blood sugar; **Hba1c,** glycated hemoglobin; **AST,** aspartate aminotransaminase**; ALT**, alanine aminotransaminase**; INR:** International Normalized Ratio; **FIB4,** Fibrosis 4 score, **APRI,** AST to platelet Ratio Index**; HARI,** hepatic artery resistive index, **LSM,** liver stiffness measurement **CAP,** controlled attenuation parameter.

Table 2: Correlation of HARI with demographic, anthropometric and biochemical parameters in studied patients.

Parameter	r	p
Age	0.42	0.0001
BMI (Kg/m2)	0.12	0.29
Waist circumference (centimeters)	0.032	0.75
Fasting blood sugar (mg/dl)	0.37	< 0.0001
Hba1c (%)	0.33	0.001
Cholesterol (mg/dl)	0.18	0.08
Triglyceride (mg/dl)	-0.1	0.31
LDL (mg/dl)	0.26	0.01
HDL (mg/dl)	0.19	0.05
AST (U/L)	0.04	0.66
ALT (U/L)	-0.02	0.84
Albumin (g/del)	-0.19	0.05
Bilirubin (mg/dl)	-0.05	0.6
INR	-0.08	0.45
Creatinine (mg/dl)	0.04	0.69
Uric acid (mg/dl)	-0.18	0.07
White blood Cells (103/µL)	-0.1	0.30
Hemoglobin	0.04	0.71
Platelets (×103/µL)	-0.08	0.41

BMI, body mass index; **2hpp,** 2 hour postprandial blood sugar; **Hba1c,** glycated hemoglobin; **AST,** aspartate transaminase**; ALT**, alanine transaminase**; LDL**, low density lipoprotein**; HDL, high density lipoprotein; INR,** international normalized ratio.

Table 3: Correlation of hepatic artery resistive index with noninvasive methods for assessment of fibrosis and steatosis.

Parameter	r	p
LSM	0.39	< 0.0001
NAFLD fibrosis score	0.37	< 0.0001
CAP	-0.22	0.03
FIB4	0.37	< 0.0001
APRI	0.131	0.195

LSM, liver stiffness measurement; CAP, controlled attenuation parameter; APRI, AST to platelet Ratio Index.

Table 4: Comparison of noninvasive methods for assessment of fibrosis between F0 group, F1-2 group and F3-4 group according to LSM values.

	F0 (<6 KP) (64)	**F1-2 (6.1–9 KP) (26)**	**F3-4 (≥ 9.1 KP) (10)**	**p**	**P1**	**P2**	**P3**
CAP	320 (247–397)	326 (276-380)	220 (133-397)	0.008	0.6	0.003	0.005
HARI	0.64 (0.5 - 0.87)	0.7 (0.6 - 0.94)	0.8 (0.69-0.87)	0.001	0.1	0.001	0.002
FIB4	0.97 (0.55 - 2.08)	1.46 (0.85 - 2.11)	1.6 (1.08 - 7.5)	< 0.0001	< 0.0001	< 0.0001	0.4
APRI	0.33 (0.16 – 1.43)	0.4 (0.24 - 1.1)	0.54 (0.27 - 3.02)	0.006	0.02	0.02	0.1
NFS	-2.03 (- 3.48 - -0.06)	-0.55 (-1.55 - 1.09)	1.76 (-2.75 - 2.11)	< 0.0001	< 0.0001	0.01	0.3

APRI: AST- Platelets Ratio Index, CAP: Controlled Attenuation Parameter, **FIB4:** Fibrosis 4 score**, HARI:** Hepatic artery Resistive index**, NFS:** NAFLD fibrosis score

A test used: Kruskalwallis test followed by Mann-whitneyy for data expressed as median and range

P: Probability

P1: Significance between F0 group & F1, 2 groups.

P2:Signifcnace between F0 group & F3, 4 groups.

P3: Significance between F1, 2 group & F3, 4 group.

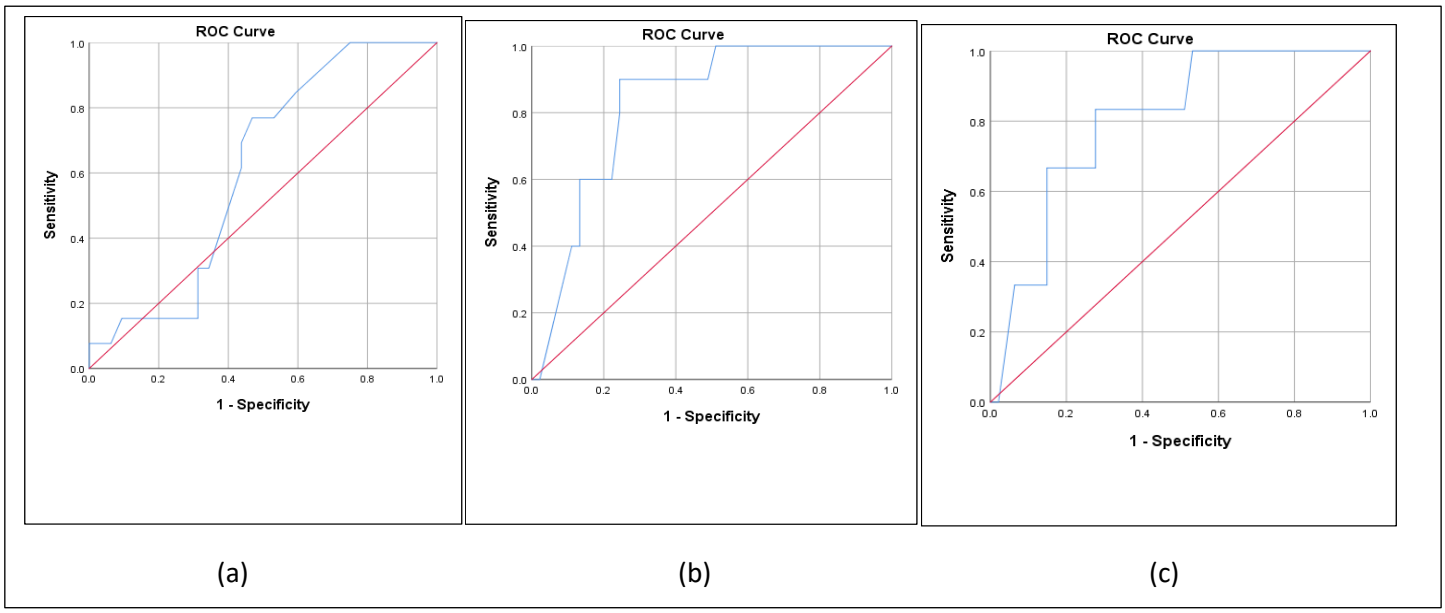

Figure 1: ROC curve of accuracy of HARI for prediction of (a) early fibrosis (6.1 - 9 KPa); (b) advanced fibrosis (> 9.1KPa) and (c) cirrhosis (≥ 10.4KPa).

Table 5: ROC curve of accuracy of HARI for prediction of early fibrosis (6.1-9 KPa), advanced fibrosis (> 9.1KPa) and cirrhosis (≥ 10.4KPa).

Prediction of fibrosis degree	HARI cutoff	AUC	P	95% CI	Sensitivity	Specificity
6.1 - 9 Kpa	0.67	0.611	0.1	(0.494 - 0.727)	69%	57%
≥ 9.1KPa	0.76	0.826	0.001*	(0.725 – 0.926)	80%	76%
≥ 10.4 KPa	0.74	0.803	0.01*	(0.659 – 0.948)	83%	72%

These results suggest that VLDL synthesis is impaired in NASH, in spite of the presence of abundant free cholesterol in the serum, due to a marked reduction in hepatic synthesis of apoB100, compared with obese (BMI-matched) controls without NASH [35] and defects in choline utilization [36]. This discrepancy could be attributed to two different numbers of patients included in the studies, baseline characteristics of patients such as ethnicity, BMI, dietary habits, degree of steatosis.

Regarding platelets, we observe no significant correlation between HARI and platelets profile. Several studies that reported a strong negative correlation of platelet count with stiffness [17,37] and also with NAFLD related liver fibrosis evaluated by non-invasive methods [38-40]. According to Olivares-Gazca et al., (24%) of patients with NAFLD without cirrhosis (as determined by TE) had thrombocytopenia [41].

The present study showed that, at cutoff point 0.76, sensitivity and specificity of HARI for prediction of advanced fibrosis (> 9.1 KPa) was 80% and 76% respectively with an area under the curve (0.826). In line with our results, according to Ergelen et al., the optimal HARI cutoff value for a significant fibrosis was > 0.75, yielding a sensitivity of 78% and a specificity of 75%, with an area under the curve of 0.90 [10]. Additionally, Doppler parameters alone, according to Alempijevic et al., predict the presence of F2 fibrosis with reasonable accuracy. Better prediction rates are obtained by combining Doppler variables with non- invasive markers and transient elastography of liver stiffness. Combining Doppler parameters, non-invasive markers (APRI, ASPRI, and FIB-4) and transient elastography yielded the best model for predicting significant fibrosis, with sensitivity and specificity of 88.9 percent and 100 percent, respectively, [28]. On the other hand, we observe less accuracy of HARI in the evaluation of early degrees of fibrosis. Sensitivity and Specificity of HARI for prediction of early fibrosis (> 6.1 and < 9.1 KPa) was 69% and 57% respectively with an area under the curve (0.611).

This study has some limitations. Firstly, a small number of cases. The second is the lack of biopsy confirmation of our findings. Thirdly, the factors which may affect the HARI evaluation include but not limited to blood pressure and medication. Finally, a cohort of HARI values of NAFLD patients is required to confirm or refute the utility of HARI in the monitoring of NAFLD-related liver fibrosis.

Conclusion

The present study revealed that HARI had better sensitivity and specificity for prediction of advanced fibrosis and cirrhosis (> 9.1 KPa). A statistically significant positive correlation of HARI with FIB4, NFS and LSM, and a significant negative correlation of HARI with CAP was detected was detected in patients with NAFLD..

Ethical approval.

Ethics committee approval was received for this study from the Institutional Review Board of Mansoura Faculty of Medicine (Code number: MD. 18.08.79; Decision Date: 27.08.2018). This research has received no outside funds.

Conflict of interest

There are no conflicts of interest declared by the authors.

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