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Renal resistive index in non-alcoholic fatty liver disease as an indicator of early renal affection

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Abstract

Background: Nonalcoholic fatty liver disease (NAFLD) is a possible risk factor for chronic kidney disease (CKD). Renal resistive index (RRI) which is a ratio of peak systolic and end diastolic velocity can test arterial stiffness and endothelial renal dysfunction. The aim of the work is to detect the relation between NAFLD and RRI as an indicator of early renal affection and its relation to the disease severity. This study included 150 subjects divided into 3 groups: patients with NASH, simple steatosis, and control group (50 patients each). All patients were subjected to full history taking, clinical examination, laboratory investigations, abdominal ultrasound examination, and RRI measurement.

Results: 6.0% of NASH patients had significant fibrosis by NAFLD fibrosis score. RRI was significantly higher in NASH patients with fibrosis (mean = 0.74) than NASH patients without fibrosis (mean = 0.65) and patients with simple steatosis (mean = 0.63). It was the lowest in normal controls (mean = 0.61). There were significant correlations between RRI and age, BMI, serum lipids, liver enzymes, and NAFLD fibrosis score. Multiple linear regression analysis found that age and serum cholesterol were significant independent factors of increased RRI ($p < 0.0001$). RRI showed low diagnostic performance in differentiation between NASH and simple steatosis using ROC curve.

Conclusion: RRI was significantly higher in NASH patients with and without hepatic fibrosis. RRI correlates significantly with NAFLD fibrosis score. RRI can be used as an indicator of early renal affection in patients with NAFLD.

Keywords: NAFLD, NASH, RRI, CKD

Background

Non-alcoholic fatty liver (NAFLD) is a fatty infiltration of the liver (steatosis) diagnosed by imaging or histology with or without inflammation or fibrosis in the absence of other causes of hepatic fatty infiltration. NAFLD is subcategorized to simple hepatic steatosis and nonalcoholic steatohepatitis (NASH). Regarding simple hepatic steatosis, there is no evidence of inflammation, but in NASH, there is inflammation of the liver [1].

NAFLD is a worldwide health problem with prevalence of 6 to 35% [2]. Regarding sex distribution of

NAFLD, studies are very different, and some studies suggest that it is more prevalent in males [3], while others suggest that it is more prevalent in females [4].

NAFLD patients (mainly NASH patients) often have at least one component of the metabolic syndrome (MS) [5]. Meanwhile, the MS is an important risk factor for cardiovascular disease (CVD) besides being common in NAFLD patients. There are recent data that support that NAFLD independently may contribute to increased risk of CVD [6].

On the other hand, chronic kidney disease (CKD) is an important health problem [7]. Nowadays, we know that cardiovascular diseases (CVD) are the main cause of morbidity and mortality in patients with CKD [8].

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Recently, NAFLD was considered as a probable risk factor for CKD development and progression [9].

CKD and NAFLD have convergent pathophysiological mechanisms and cardiometabolic risk factors. CKD and NAFLD pathogenesis may be due to insulin resistance (IR), rennin-angiotensin system (RAS) activation, oxidative stress, and inappropriate secretion of cytokines by the inflamed and steatotic liver. The expected link between the kidney and liver is seen in patients with liver cell failure (LCF) as hepatorenal syndrome [10]. Targher et al. performed two cross-sectional studies which declared that CKD prevalence is higher in NAFLD patients than in others without steatosis [11, 12].

Renal resistive index (RRI) is a semi-quantitative index obtained by Doppler evaluation of renal vascular bed. $RRI = [(peak\ systolic\ velocity - end\ diastolic\ velocity) \div peak\ systolic\ velocity]$. The value of RRI is in the range of 0.47–0.70, and it usually shows a difference between the two kidneys of less than 5–8% [13].

RRI role has been extensively investigated among various kidney diseases as an early test of arterial stiffness and endothelial dysfunction which may lead to severe end-organ disease, due to its known correlations with histological parameters, as tubulointerstitial lesions and glomerulosclerosis [14, 15].

The present study aimed to detect the relation between non-alcoholic fatty liver disease and renal resistive index as an indicator of early renal affection, with correlation between it and the disease severity.

Methods

This prospective observational case control study was conducted on 150 individuals. The enrolled individuals were divided into 3 groups. Group 1 included 50 patients with NASH with or without fibrosis, group 2 included 50 patients with simple steatosis, and group 3 included another 50 normal healthy individuals as controls.

All patients and controls (age > 18 years) were collected from the outpatient clinic of the Internal Medicine Department, Ain Shams University Hospitals, Cairo, Egypt, during the period from January 2016 to May 2016.

Detailed medical history taking and thorough physical examination were done to all participants and controls. They were subjected to laboratory workup, in the form of liver function tests including aspartate aminotransferase (AST), alanine aminotransferase (ALT), total and direct bilirubin (T. and D. Bil.), serum albumin, total proteins (total prot.), gamma glutamyl transferase (GGT), and alkaline phosphatase (ALP); viral markers including hepatitis B surface antigen (HBsAg) and hepatitis C antibodies (HCV Ab); lipid profile including total cholesterol, triglycerides (TG), low-density lipoproteins

(LDL), and high-density lipoproteins (HDL); renal function tests including serum creatinine (SCr), blood urea nitrogen (BUN), serum sodium (Na), potassium (K), estimated glomerular filtration rate (eGFR), and complete urine analysis; and fasting blood glucose (FBG).

Radiological assessment, by a single professional radiologist, using an abdominal U/S was done for all patients and controls included in the study after fasting for 8 h. They were examined using ultrasound (U/S) equipment with color Doppler capability and 2.8–5 MHz convex linear transducer (LOGIQ P6, GE Medical Systems, USA) for the evaluation of liver size, capsular contour (smooth, coarse, lobulated), and parenchymal echogenicity. The kidney size, cortical thickness (not less than 10 mm), cortico-medullary differentiation, and echogenicity were assessed. The U/S equipment automatically calculated the RRI. Intra-renal resistance was recorded at interlobar arteries in three different regions of both kidney (superior, middle, and inferior zones), and the mean value was calculated. Then, a mean RRI was calculated derived from 6 measurements for each patient.

RRI formula: $RRI = (peak\ systolic\ velocity - end\ diastolic\ velocity) / peak\ systolic\ velocity$ [16].

The sonographic picture of increased liver echogenicity together with normal or elevated liver enzymes was used for differentiation between simple steatosis and NASH, while the assessment of the presence of fibrosis in NAFLD non-invasively was done by calculating the NAFLD fibrosis score [17]. This score required the following data: age, body mass index (BMI), AST, ALT, albumin, platelet count, and fasting blood sugar.

NAFLD fibrosis score formula

$-1.675 + 0.037 \times age\ (years) + 0.094 \times BMI\ (kg/m^2) + 1.13 \times IFG/diabetes\ (yes = 1, no = 0) + 0.99 \times AST/ALT\ ratio - 0.013 \times platelet\ (\times 10^9) - 0.66 \times albumin\ (g/dL)$.

The results were interpreted as follows:

- < -1.455 : predictor of absence of significant fibrosis (F0-F2 fibrosis)
- ≥ -1.455 to ≤ 0.675 : indeterminate score
- > 0.675 : predictor of presence of significant fibrosis (F3-F4 fibrosis)

Patients with any structural or functional renal disease such as renal artery stenosis or acute or chronic renal diseases, patients receiving any nephrotoxic drugs, patients with diabetes mellitus or hypertension, and patients with any other liver diseases rather than NAFLD were excluded from the study. Controls were collected from those with irrelevant medical history, normal physical examination and body mass index, normal liver echogenicity, contour and size, normal liver and kidney function tests, and normal eGFR and urine analysis.

The study was performed according to the ethical guidelines of the 1975 Declaration of Helsinki. A written informed consent was obtained from all enrolled participants before enrolment to the study. This study was approved by the ethical committee of Faculty of Medicine, Ain Shams University.

Statistical methods

The collected data were coded, tabulated, and statistically analyzed using IBM SPSS statistics (Statistical Package for Social Sciences) software version 22.0, IBM Corp., Chicago, USA, 2013. Descriptive statistics were done using minimum and maximum of the range as well as mean \pm SD (standard deviation) for quantitative normally distributed data, while it was done for qualitative data as number and percentage. Inferential analyses were done for quantitative variables using ANOVA test with post hoc Tukey test for more than two independent groups with normally distributed data. For qualitative data, inferential analyses for independent variables were done using chi square test for differences between proportions with post hoc Bonferroni test. Pearson correlation was used for numerical normally distributed data. ROC curve was used to evaluate the performance of different tests to differentiate between certain groups. Linear regression model was used to find out the independent factors affecting certain conditions. The level of significance was taken at P value < 0.05 .

Results

Twenty-one, 24, and 26% of groups 1, 2, and 3 were males. The mean age of patients of groups 1, 2, and 3 was 51 ± 8.7 , 49.1 ± 9.8 , and 50.1 ± 10.5 years, respectively. BMI was significantly lower in the control group with no significant difference between NASH and simple steatosis groups (Table 1).

FBG and lipid profile were significantly higher, while HDL was significantly lower among the NASH group. Liver enzymes were significantly higher in NASH group with no significant difference between control and simple steatosis groups. Serum albumin was significantly higher in the control group with no significant difference between NASH and simple steatosis groups. Creatinine and BUN were within the normal ranges in all groups but showed significantly higher levels among NASH, followed by simple steatosis then the controls. eGFR was significantly highest in the control group with no significant difference between NASH and simple steatosis groups. RRI was significantly higher among NASH patients in comparison with the other two groups (Table 1).

NAFLD fibrosis score was significantly higher among NASH patients, followed by simple steatosis and lowest among controls. Higher number and percentage of

patients with liver fibrosis were found in NASH patients (Table 2, Fig. 1).

There were significant positive correlations between RRI on one side and age and BMI on the other side. Also, there were significant positive correlations between RRI and cholesterol, triglycerides, ALT, AST, ALP, GGT, and liver fibrosis score. There was significant negative correlation between RRI and HDL. There was significant positive correlation between RRI and serum creatinine, and a significant negative correlation between RRI and eGFR. There was non-significant correlation between RRI and BUN, serum Na, and K (Table 3).

Age and cholesterol were found to be significant factors that increase RRI by logistic regression analysis (Table 4). RRI had significant low diagnostic performance in differentiation between NASH patients with or without fibrosis from patients with simple steatosis (Table 5, Fig. 2).

RRI was higher in NASH patients with fibrosis (mean = 0.74) than NASH patients without fibrosis (mean = 0.65) and patients with simple steatosis (mean = 0.63). It was the lowest in normal controls (mean = 0.61).

Discussion

The aim of this study was to find the relation between non-alcoholic fatty liver disease and renal resistive index as an indicator of an early renal affection with correlation between it and the disease severity determined by NAFLD fibrosis score.

In this study, there was no significant difference between the studied groups regarding demographic characteristics. These findings are consistent with Corey et al. who stated that there were no differences in mean age in NAFLD patients and others [18]. Higher body mass index was found in patients with NASH and simple steatosis in the current study. Fierbinteanu-Braticevici et al. stated that simple steatosis and NASH are associated with high BMI. They also found an association between old age and NASH [19]. On the other hand, Nugent and Younossi stated that NAFLD and NASH may be present in lean subjects having normal BMI and they may be absent in subjects having a high BMI [20].

Fasting blood glucose (FBG) was significantly higher in NASH group than simple steatosis and control groups in the current study. These results are consistent with Jimba et al. who found that NAFLD had a significant positive association with increasing FBG in non-diabetic individuals [21].

Total cholesterol, LDL, and TG were significantly higher, while HDL was significantly lower among NASH group than simple steatosis and control groups. These results are consistent with Puri et al., Miura and Ohnishi, and Mahaling et al. who stated that, in NAFLD, serum total cholesterol, TG, and

Table 1 Comparison between the three groups regarding the studied variables using ANOVA test

Variables		Group 1 (N = 50)	Group 2 (N = 50)	Group 3 (N = 50)	P	
BMI (kg/m ²)	Mean ± SD	29.3 ± 2.5	29.1 ± 1.6	22.0 ± 1.5	< 0.001*	
	Range	24.0–34.3	25.5–34.5	18.2–24.5		
	HG	a	a	b		
FBG (mg/dL)	Mean ± SD	88.8 ± 5.6	84.4 ± 6.7	77.3 ± 5.9	< 0.001*	
	HG	a	b	c		
Lipid profile	Cholesterol (mg/dL)	Mean ± SD	251.8 ± 38.1	224.8 ± 26.2	157.1 ± 27.1	< 0.001*
		HG	a	b	c	
	TG (mg/dL)	Mean ± SD	225.2 ± 59.2	198.8 ± 36.5	117.2 ± 17.5	< 0.001*
		HG	a	b	c	
	LDL (mg/dL)	Mean ± SD	194.8 ± 22.7	182.2 ± 16.3	106.2 ± 25.6	< 0.001*
		HG	a	a	b	
	HDL (mg/dL)	Mean ± SD	37.4 ± 4.1	41.1 ± 5.2	49.8 ± 10.8	< 0.001*
		HG	a	b	c	
	ALT (IU/L)	Mean ± SD	78.81 ± 17.8	25.7 ± 7.9	24.0 ± 7.2	< 0.001*
		HG	a	b	b	
	AST (IU/L)	Mean ± SD	69.4 ± 16.7	23.8 ± 6.9	23.4 ± 6.9	< 0.001*
		HG	a	b	b	
	ALP (IU/L)	Mean ± SD	128.1 ± 31.6	71.9 ± 23.7	61.9 ± 14.7	< 0.001*
		HG	a	b	b	
	GGT (IU/L)	Mean ± SD	75.1 ± 18.3	34.1 ± 8.1	31.8 ± 9.6	< 0.001*
		HG	a	b	b	
	D. Bil. (mg/dL)	Mean ± SD	0.60 ± 0.13	0.60 ± 0.12	0.62 ± 0.12	0.559
	T. Bil. (mg/dL)	Mean ± SD	0.16 ± 0.05	0.15 ± 0.05	0.15 ± 0.05	0.730
	Albumin (gm/dL)	Mean ± SD	4.04 ± 0.20	4.11 ± 0.21	4.22 ± 0.28	< 0.001*
		HG	a	a	b	
	Tot. Proteins (gm/dL)	Mean ± SD	7.29 ± 0.32	7.32 ± 0.34	7.36 ± 0.34	0.630
	Creatinine (mg/dL)	Mean ± SD	0.87 ± 0.11	0.73 ± 0.14	0.66 ± 0.13	< 0.001*
		HG	a	b	c	
	BUN (gm/dL)	Mean ± SD	14.9 ± 2.3	13.2 ± 2.9	11.5 ± 2.8	< 0.001*
		HG	a	b	c	
	eGFR (mL/min)	Mean ± SD	117.5 ± 5.1	118.8 ± 5.0	122.0 ± 5.3	< 0.001*
		HG	a	a	b	
	Na (mmol/L)	Mean ± SD	140.3 ± 2.3	140.2 ± 1.9	139.7 ± 1.8	0.294
	K (mmol/L)	Mean ± SD	4.13 ± 0.28	4.17 ± 0.31	4.07 ± 0.20	0.200
RRI	RRI	Mean ± SD	0.66 ± 0.04	0.63 ± 0.04	0.61 ± 0.04	< 0.001*
		Range	0.65–0.67	0.62–0.64	0.60–0.62	
		95% CI	0.65–0.67	0.62–0.64	0.60–0.62	
		HG	a	b	c	

CI confidence interval, HG homogenous groups (have the same letter by post hoc test). *Significant

LDL cholesterol show a stepwise increase from simple steatosis to NASH, while HDL cholesterol was lower in NASH patients followed by simple steatosis patients and highest in normal [22–24].

No significant difference was found between the studied groups regarding Na and K in the present study. Sun

et al. and Tabbaa et al. stated that low serum potassium levels were associated with disease severity in NAFLD patients [25, 26].

ALT, AST, ALP, and GGT were significantly higher in NASH group with no significant difference between control and simple steatosis groups in the current study.

Table 2 NAFLD fibrosis score among the studied groups

Variables		Group 1 (N = 50)	Group 2 (N = 50)	Group 3 (N = 50)	P
Score	Mean ± SD	- 1.31 ± 0.95	- 2.15 ± 0.78	- 3.30 ± 0.74	^< 0.001*
	Range	- 3.50-0.68	- 4.00 to - 0.44	- 5.00 to - 1.8	
	HG	a	b	c	
Grade (n, %)	No fibrosis	31 (62.0%)	43 (86.0%)	50 (100.0%)	# 0.014*
	Intermediate score	16 (32.0%)	7 (14.0%)	0 (0.0%)	
	Fibrosis	3 (6.0%)	0 (0.0%)	0 (0.0%)	
	HG	a	b	c	

^ANOVA, #chi square test, *Significant

Frantzides et al. and Puri et al. stated that the values of AST and ALT were higher in NASH patients followed by simple steatosis patients and were the lowest in normal controls [22, 27]. Puri et al. stated that mean ALP was higher in NASH patients followed by NAFLD patients and was the lowest in normal controls [22]. Fierbinteanu–Braticevici et al. and Shen et al. found that GGT was high in NAFLD patients and increased with the severity of liver affection [20, 28].

In the present study, no significant difference was found between the study and control groups regarding serum bilirubin and total protein. Kwak et al., Hjelkrem et al., Chang et al., and Tian et al. stated that serum bilirubin levels were inversely associated with NAFLD prevalence [29–32]. On the other hand, Puri et al. stated that total bilirubin was higher in NAFLD patients and increasing with the severity of liver affection [22].

Liver fibrosis score was significantly higher among NASH group. In NASH group, 62.0% of patients had no significant fibrosis, 32.0% of patients had indeterminate scores, and 6.0% of patients had significant fibrosis. In simple steatosis group, 86.0% of patients had no significant fibrosis, and 14.0% of patients had indeterminate

scores. All the included subjects in the control group had no fibrosis. In agreement with the current study, Williams et al. stated that 7% of NAFLD patients who underwent liver biopsy had significant fibrosis [3]. Also, Wong et al. stated that the prevalence of significant fibrosis in NAFLD patients was 4% and unlikely to exceed 10% [33].

RRI was significantly higher in the NASH group than those with simple steatosis who were higher than the control group. In NASH patients, RRI was higher among those with hepatic fibrosis (mean = 0.74) than in those without fibrosis (mean = 0.65). Catalano et al. stated that they did not find a significant difference in RRI between NAFLD patients and normal controls. Also, they did not find a significant difference between NAFLD patients with normal levels of liver enzymes and those with high levels of liver enzymes [34].

In the current study, there were significant positive correlations between RRI and age, BMI, cholesterol, triglycerides, ALT, AST, ALP, GGT, and liver fibrosis. On the other hand, there was significant negative correlation between RRI and HDL. Using multiple linear regression analysis, age and cholesterol were found to be significant

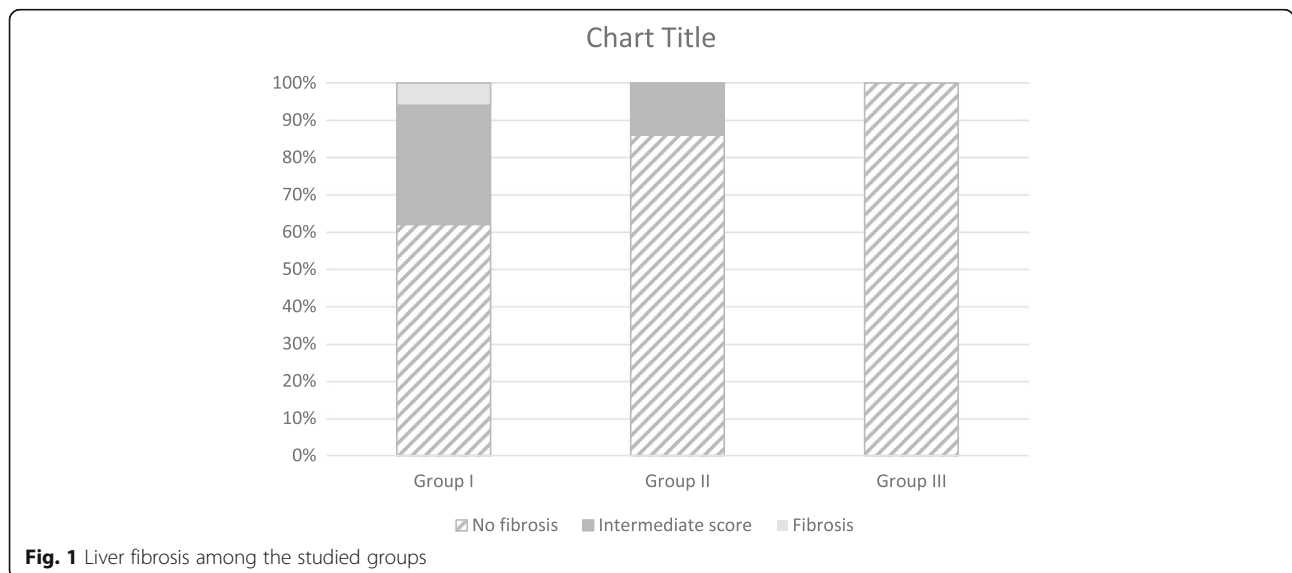


Fig. 1 Liver fibrosis among the studied groups

Table 3 Correlation between RRI and demographic and laboratory variables among the studied groups using Pearson correlation

Variables		Group 1 (N = 50)		Group 2 (N = 50)		Group 3 (N = 50)	
		r	p	r	p	r	p
Demographic	Age	0.634	< 0.001*	0.466	< 0.001*	0.644	< 0.001*
	BMI	0.826	< 0.001*	0.408	< 0.003*	0.648	< 0.001*
	FBG	0.102	0.480	0.109	0.449	0.040	0.784
Lipid profile	Cholesterol	0.405	0.004	0.344	0.014	0.513	< 0.001*
	TG	0.424	0.002*	0.303	0.047*	0.624	< 0.001*
	LDL	0.204	0.155	0.227	0.102	0.373	0.108
	HDL	-0.443	< 0.001*	-0.615	< 0.001*	-0.314	0.026
Liver profile	ALT	0.12428	0.002	0.449	< 0.001*	0.373	0.008
	AST	0.458	< 0.001*	0.376	0.007*	0.316	0.025*
	ALP	0.373	< 0.001*	0.338	0.046*	0.495	< 0.001*
	GGT	0.307	0.030*	0.416	0.003*	0.269	0.049*
	T. Bil	0.051	0.723	0.031	0.833	-0.055	0.706
	D. Bil	-0.004	0.978	0.031	0.830	-0.063	0.665
	Albumin	-0.584	< 0.001*	-0.467	< 0.001*	-0.407	0.046
	Total protein	-0.485	< 0.001*	-0.555	< 0.001*	-0.415	0.019
Kidney functions	Creatinine	0.480	< 0.001*	0.356	0.011*	0.301	0.034*
	eGFR	-0.593	< 0.001*	-0.512	< 0.001*	-0.495	< 0.001*
Liver fibrosis	Score	0.851	< 0.001*	0.851	< 0.001*	0.532	< 0.001*

*Significant

independent factors of higher RRI. RRI showed low diagnostic performance in differentiation between patients with NASH and liver fibrosis and those with simple steatosis. Ponte et al. stated that higher BMI and age were associated with higher RRI values. Also, they stated that age is one of the significant determinants of the RRI in the general population, but they highlighted a nonlinear association between age and RRI [35].

The expanded and inflamed visceral adipose tissue mass is a source of multiple factors that are potentially involved in the process of atherogenesis and the development of insulin resistance, NAFLD, and

possibly the cardiac and renal affection. These factors include free fatty acids (FFA), hormones, and proinflammatory adipocytokines [36]. Hepatic steatosis leads to subacute intrahepatic inflammation through activation of nuclear factor-κB pathways that exacerbate insulin resistance both locally in the liver and systematically [37]. NAFLD is associated with increased levels of circulating proinflammatory markers such as C reactive protein, interleukin (IL) 6, tumor necrosis factor (TNF)-α, and other hepatic acute-phase proteins, procoagulant factors as fibrinogen, plasminogen activator inhibitor-1, factor VIII, and adhesion molecules like vascular adhesion protein-1 that are likely to have been synthesized within the liver, especially in the presence of NASH, together with impaired fibrinolysis (e.g., high levels of PAI-1) [38]. These proinflammatory and procoagulant factors were found to be highest in patients with NASH, intermediate in those with simple steatosis, and lowest in age, sex, and weight-matched control individuals without steatosis [39]. These risk factors could explain the cardiac and renal affection in NAFLD.

Table 4 Linear logistic models for factors affecting RRI among the studied groups

Variables	B	SE	p	95% CI	R ²
Group 1					
Age	0.0042	0.0004	< 0.001*	0.0033–0.0051	0.998
Cholesterol	0.0006	0.0001	< 0.001*	0.0004–0.0008	
Group 2					
Age	0.0027	0.0007	< 0.001*	0.0013–0.0040	0.995
Cholesterol	0.0007	0.0002	0.004*	0.0002–0.0012	
Group 3					
Age	0.0024	0.0005	< 0.001*	0.0014–0.0034	0.997
Cholesterol	0.0008	0.0002	< 0.001*	0.0004–0.0011	

β regression coefficient, SE standard error, CI confidence interval, R² coefficient of determination, *significant

Table 5 Diagnostic performance of RRI in prediction of NASH

Groups	AUC	SE	p	95% CI
Group 1 from 2	0.692	0.054	< 0.001*	0.586–0.798

AUC area under curve, SE standard error, CI confidence interval, *significant

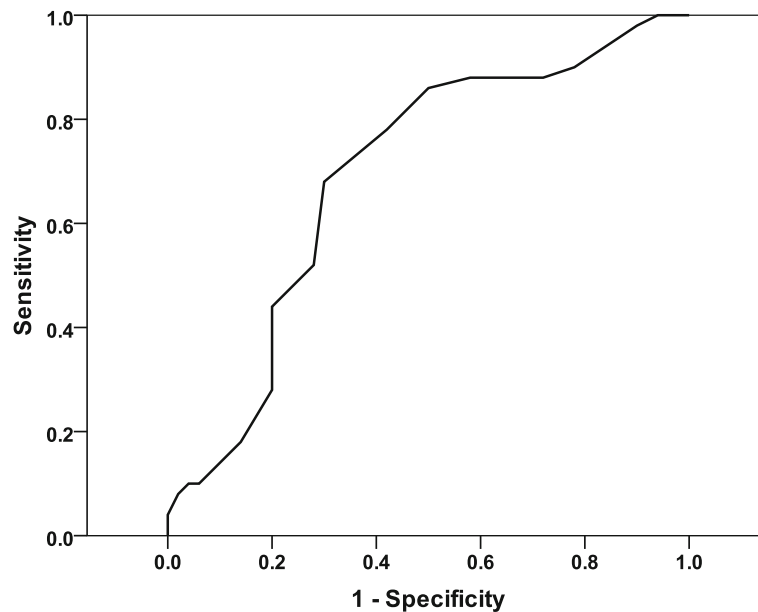


Fig. 2 ROC curve for RRI in differentiation between NASH patients and simple steatosis

Conclusion

NAFLD is associated with higher blood sugar, hazardous serum lipids, and liver enzymes. RRI was significantly higher in NASH patients with and without hepatic fibrosis. RRI correlated significantly with NAFLD fibrosis score, liver enzymes, and serum lipids.

Abbreviations

ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CKD: Chronic kidney disease; CVD: Cardiovascular disease; D. Bil.: Direct bilirubin; FBG: Fasting blood glucose; GGT: Gamma glutamyl transferase; HBsAg: Hepatitis B surface antigen; HCV Ab: Hepatitis C antibodies; HDL: High-density lipoproteins; IFG: Impaired fasting glucose; IR: Insulin resistance; LCF: Liver cell failure; LDL: Low-density lipoproteins; MS: Metabolic syndrome; NAFLD: Nonalcoholic fatty liver disease; NASH: Nonalcoholic steatohepatitis; RAS: Rennin-angiotensin system; RRI: Renal resistive index; SD: Standard deviation; SPSS: Statistical Package for Social Sciences; T.Bil.: Total bilirubin; TG: Triglycerides

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Authors' contributions

Dr. 'HM' and Dr. 'WY' contributed in the revision of the work and in the acceptance of the final form of the manuscript. Dr. 'SS' contributed in conception and the design of the work, writing of the manuscript, and revision of the work. Dr. 'MEB' contributed in writing of the manuscript and revision of the work. Dr. 'AH' contributed in the conception and the design of the work together with performing the clinical part and revising the manuscript. Dr. 'MS' and 'HM' contributed in collection of the data and in performing the statistical part of the work. All authors have read and approved the manuscript.

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Availability of data and materials

All data and materials are available.

Ethics approval and consent to participate

The study was performed according to the ethical guidelines of the 1975 Declaration of Helsinki. A written informed consent was obtained from all enrolled participants before enrolment to the study. This study was approved by the ethical committee of Faculty of Medicine, Ain Shams University (committee's reference number: 122/2016).

Consent for publication

Not applicable.

Competing interests

None of the authors have any conflicts of interests or financial disclosures related to this work.

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