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Liver stiffness, hepatorenal index, and microRNA-130b as predictors for chronic kidney disease in patients with non-alcoholic fatty liver disease

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Abstract

Background and aim Currently, nonalcoholic liver disease (NAFLD) is the most predominant chronic liver disorder. NAFLD has been linked to hepatic and extrahepatic morbidities. We aimed to investigate the role of acoustic radiation force impulse (ARFI), hepatorenal index (HRI), and serum microRNA-130b as non-invasive predictors for chronic kidney disease (CKD) in NAFLD patients.

Material and methods In a case–control design, we included 40 NAFLD patients (20 NAFLD with CKD and 20 NAFLD without CKD) and 20 healthy controls. After clinical evaluation, laboratory assessments including liver test profile, renal function test, and quantification of microRNA-130b were done. Liver steatosis and stiffness were evaluated using HRI and ARFI.

Results HRI and ARFI readings were significantly higher among NAFLD with CKD patients compared to other groups ($P < 0.001$). The median values of microRNA-130b were 32.1, 27.01, and 25.36 copies/μl in NAFLD with CKD, NAFLD without CKD, and healthy controls, respectively, with significant differences between groups ($P < 0.05$). ARFI values and HRI were positively correlated with microRNA-130b ($P < 0.05$). At a cutoff value > 28.13 copies/μl, microRNA-130b could differentiate between "NAFLD with CKD" and "NAFLD without CKD" patients with a sensitivity and specificity of 75% and 70%, respectively ($AUC = 71.9\%$, $P = 0.018$).

Conclusions Serum microRNA-130b, HRI, and ARFI are valuable noninvasive markers for the assessment of NAFLD. MicroRNA-130b is suggested as a sensitive biomarker for the prediction of CKD among NAFLD patients with good sensitivity and specificity.

Keywords MicroRNA-130b, Hepatorenal index, NAFLD; Chronic kidney disease, Elastography

Introduction

Currently, non-alcoholic liver disease (NAFLD) is the most predominant chronic liver disorder worldwide [1]. NAFLD progression to fibrosis is affected by several factors including insulin resistance (IR), lipotoxicity, gut microbiota, oxidative stress, and genetic factors [2, 3]. Noninvasive diagnosis of NAFLD can be achieved by many tools, including the acoustic radiation force impulse (ARFI) which uses short-duration acoustic

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pulses, transient elastography (TE), and the hepatorenal index [4–6]. There is growing evidence that the synthesis and release of pro-inflammatory cytokines in NAFLD are connected to the development of chronic kidney disease (CKD) among NAFLD patients [7]. The prevalence of CKD in patients with NAFLD ~ 20–55%. The coexistence of NAFLD and CKD has a deleterious impact on outcomes, especially cardiovascular morbidity and mortality. So, the early recognition and screening for CKD in NAFLD patients are of clinical importance to allow for earlier introduction of relevant strategies [8].

Recently, microRNAs (miRNAs) have been of growing public interest [9]. A miRNA is a form of small, single-stranded RNA, 18–25 nucleotides, which is transcribed from DNA, instead of being translated into protein, and modulates the functions of other genes in protein synthesis [10]. MicroRNAs have been linked to manipulating vital renal functions. The progression of renal illnesses such as diabetic kidney disease (DKD), acute kidney injury, lupus nephritis, and polycystic kidney disease has been linked to changes in the expression of microRNAs. In addition, microRNAs have potential diagnostic and therapeutic targets. MicroRNA-21, miRNA-192, and miRNA-29 were found to be involved in the pathogenesis of DKD and could be employed as DKD biomarkers [11, 12]. We aimed to investigate microRNA 130b as a potential noninvasive biomarker for the early detection of CKD among NAFLD patients.

Subjects and methods

In a case–control design, we included 40 NAFLD patients (20 patients with CKD "group I" and 20 patients without CKD "group II"). An age- and sex-matched 20 healthy subjects were included in "group III." Patients were recruited from the Internal Medicine Department, Faculty of Medicine, Alexandria University. The diagnosis of NAFLD was based on the evidence of hepatic steatosis by ultrasound (elevated hepatorenal echogenicity, vascular blurring of portal or hepatic veins) [4] and the absence of secondary factors hepatic fat accumulation (e.g., alcohol consumption, viral hepatitis, steatogenic drugs, or monogenic inherited disorders) [13].

The definition of CKD was based on either of the following presents for > 3 months [14]: (a) markers of kidney damage (one or more): [albuminuria (albumin excretion rate (AER) ≥ 30 mg/24 h or equivalent albumin-to-creatinine ratio (ACR) ≥ 30 mg/dl, urine sediment abnormalities such as isolated microscopic hematuria with dysmorphic red blood cells, red oval fat bodies or fatty casts, white blood cell casts, blood cell casts, granular casts or renal tubular epithelial cells], b) Glomerular filtration rate (GFR) < 60 ml/min/1.73 m2.

Exclusion criteria

We excluded patients with age > 50 years, diabetes mellitus, systemic hypertension, viral hepatitis C and/or B, autoimmune liver diseases, metabolic liver diseases, alcohol consumption, hepatocellular carcinoma or other malignancies, history of liver or kidney transplantation, known patients with CKD, or structural kidney abnormalities (e.g., severe renal cortical scarring, incidental large or numerous renal cysts or solid mass lesions) due to any other causes, hematological diseases, pregnancy, urinary tract disorders, and prostatic disorders (in men). Also, patients on nephrotoxic or steatogenic drugs (e.g., amiodarone, methotrexate, tamoxifen, corticosteroids, valproate) were not included. To avoid non-reliable ARFI measurements, patients with $BMI > 30$ kg/m^2 were excluded [6].

All participants were subjected to history taking, physical examination, and anthropometric measure calculations. Complete hemogram, serum aspartate and alanine aminotransferases (AST and ALT), liver profile, lipid profile, fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), serum creatinine, uric acid, and blood urea nitrogen, urine analysis, and urinary albumin creatinine ratio (uACR) were measured. Quantification of microRNA-130b expression using real-time quantitative reverse transcription PCR was done using miRNA easy Mini Kit (Qiagen, Germany) [15]. Acoustic radiation force impulse (ARFI) imaging and hepatorenal index (HRI) assessment via hepatic ultrasonography by a single experienced radiologist were done using a Siemens Acuson S2000 US System (Mochida Siemens Medical System, Tokyo, Japan) following the guidance on technique as described elsewhere. Caution was observed with placing the region of interest within the renal parenchyma while avoiding renal sinus fat, perinephric fat, and areas of artifacts [6, 16]. Hepatic steatosis was classified as mild (HRI of 1.05–1.24), moderate (HRI of 1.25–1.64), and severe (HRI > 1.65) [5].

Statistical analysis

Analysis was done by Statistical Package for Social Sciences (SPSS version 26.0) software. The normality of the data was evaluated. The data were expressed as mean ± SD, median (minimum–maximum), or proportions as appropriate. Student's *t*-test or the Mann–Whitney *U*-test to compare means was used as appropriate. A comparison between proportions was determined by the chi-square (χ^2) test or Fisher's exact test (FET). ANOVA test with post hoc was used as appropriate. Correlation between different parameters in each group was done using Spearman correlation. The sensitivity and specificity of microRNA-130b were evaluated by receiver

operating characteristic curve (ROC) analysis. Statistical significance was assessed at $P \leq 0.05$. All calculated *P*-values were two-tailed.

Results

Demographic data

Age and sex showed no statistically significant difference in the different studied groups. The median values of BMI were 29.5 kg/m^2, 28.0 kg/m^2, and 24.6 kg/m^2 for groups I, II, and III, respectively, with a statistical significance difference ($P=0.045$). Table 1 shows the baseline clinico-laboratory data of the three study groups with their statistical significance.

Hepatorenal index (HRI)

The median values of HRI were 1.5, 1.3, and 1.02 in groups I, II, and III respectively. There was a statistically significant difference between groups I and II ($P<0.001$), groups I and III ($P<0.001$), and groups II and III ($P=0.002$) as regards HRI readings (Table 2).

Acoustic radiofrequency impulse (ARFI)

The median value of ARFI was 2.97 m/s, 2.45 m/s, and 1.84 m/s in groups I, II, and III, respectively. There was a statistically significant difference between groups I and II ($P=0.002$), between groups I and III ($P<0.001$), and between groups II and III as regards ARFI ($P<0.001$) (Table 2).

Table 1 Comparison between the three studied groups according to demographic data and laboratory data

Demographic data	Group I ($n=20$)	Group II ($n=20$)	Group ($n=20$)	*p*
Gender				
Male	9 (45%)	10 (50%)	11 (55%)	0.819*
Female	11 (55%)	10 (50%)	9 (45%)	
Age (years)	45.5 (27–50)	44 (22–50)	42 (25–49)	0.111
Weight (kg)	80 (72–98)[2]	78.5 (65–98)	74 (55–92)	0.029
Height (cm)	1.65 (1.62–1.80)	1.68 (1.58–1.84)	1.71 (1.6–180)	0.373
WC (cm)	84 (75–100)[2]	80 (76–101)	77 (65–98)	0.035
BMI (kg/m^2)	29.5 (27.1–30.2)[2]	28 (22.30–30)[3]	25.5 (21.5–28.3)	< 0.001
Hemoglobin (g/dl)	11.9 (9.9–14.4)[1,2]	13.8 (11–16.6)	13.7 (11–15.8)	0.006
Platelets (x 10^3)	297 (155–433)	285.5 (195–500)	274.5 (195–410)	0.746
WBCs (x 10^3)	7.41 (4 4–11.2)	6.41 (2.96–10.8)	6.3 (4.24–10.5)	0.113
AST (IU/l)	32.5 (18–44)[2]	27.5 (10–73)[3]	18 (11–24)	< 0.001
ALT (IU/l)	42 (16–65)[2]	29 (11–94)[3]	19 (11–25)	< 0.001
Albumin (mg/dl)	3.55 (2.60–44)[1,2]	4.40 (3.70–4.7)	4.35 (3.30–4.7)	< 0.001
Bilirubin (mg/dl)	0.1 (0.22–1.2)	0.99 (0.28–1.48)	0.96 (0.54–1.10)	0.593
INR	1 (0.90–1.20)[1,2]	1 (0.90–1.10)	1 (0.96–1.0)	0.006
GGT (U/l)	37.5 (20–45)[1,2]	28 (14–40)[3]	19.5 (11–30)	< 0.001
Total cholesterol (mg/dl)	197 (132–286)[2]	195.5 (128–230)[3]	135.5 (115–154)	< 0.001
LDL-C (mg/dl)	161.50 (90–220)[1,2]	145.5 (67–170)[3]	80.50 (61–100)	< 0.001
HDL-C (mg/dl)	44 (24–66)[2]	51 (33–73)	59.5 (30–90)	0.007
Triglycerides (mg/dl)	163 (63–731)[2]	146 (60–252)[3]	86.5 (47–141)	< 0.001
FBS (mg/dl)	98 (79–104)	92.5 (80–108)	93 (80–100)	0.376
HBA1c	5.5 (5.1–5.7)[2]	5.35 (4.4–5.7)[3]	4.65 (4.1–5)	< 0.001
Serum urea (mg/dl)	5.5 (20–98)[1,2]	29 (18–45)	26.5 (20–33)	0.001
Creatinine (mg/dl)	1.84 (0.7–3)[1,2]	0.90 (0.6–1.18)	0.78 (0.58–1.10)	< 0.001
Uric acid (mg/dl)	6.35 (3.9–8)[1,2]	5.05 (3.4–8)[3]	3.30 (3–5)	< 0.001
Urine RBCs cast	5 (3–10)	3 (3–7)	4 (3–7)	0.076
Urine WBCs cast	6 (3–10)	5 (5–7)	6 (4–10)	0.946
uACR (mg/g)	50.30 (15–113)[1,2]	16.6 (9.01–29)[3]	6.85 (2.1–12)	< 0.001

ALT, alanine aminotransferase; *AST*, aspartate aminotransferase; *FBS*, fasting blood sugar; *HBA1c*, glycated hemoglobin; urine RBCs cast, urine red blood cells cast; urine WBCs cast, urine white blood cells cast; *uACR*, urinary albumin creatinine ratio. *Chi-square test. [1]*P*-value for comparing groups 1 and 2. [2]*P*-value for comparing groups 1 and 3. [3]*P*-value for comparing groups II and III. *P* statistically significant at $P \leq 0.05$. Group I, patients with NAFLD with CKD, patients with NAFLD without CKD, group III, control

Table 2 Comparison between the three studied groups according to radiological findings and microRNA-130b levels

	Group I ($n=20$)	Group II ($n=20$)	Group III ($n=20$)	p*
Liver steatosis				
Normal	0 (0%)	0 (0%)	20 (100%)	< 0.001
Mild	10 (50%)	7 (35%)	0 (0%)	
Moderate	10 (50%)	13 (65%)	0 (0%)	
HRI	1.5 (1.20–2.28)[1,2]	1.3 (1.07–1.66)[3]	1.02 (1.01–1.05)	< 0.001
ARFI (m/s)	2.97 (2.08–3.68)[1,2]	2.45 (1.85–3.81)[3]	1.84 (1.23–2.35)	< 0.001
miRNA-130b copies/μl	32.1 (24–41.7)[1,2]	27.01 (22–36)[3]	24.6 (20.2–29.8)	< 0.001

HRI, hepatorenal index; *ARFI*, acoustic radiation force impulse. [1]*P*-value for comparing groups I and II. [2]*P*-value for comparing groups I and III. [3]*P* = value for comparing groups II and III. *Statistically significant at $P \leq 0.05$. Group I, patients with NAFLD with CKD; group II, patients with NAFLD without CKD; group III, control

MicroRNA-130b

The median value of microRNA-130b was 32.1 copies/μl, 27.01 copies/μl, and 25.36 copies/μl in groups I, II, and III, respectively. There was a significant difference between groups I and II ($P=0.032$), groups I and III ($P<0.001$), and groups II and III ($P=0.045$) as regards microRNA-130b levels (Table 2).

Correlation analysis

In the current study, a positive correlation was found between HRI and ARFI in NAFLD patients with CKD ($P<0.001$). In addition, HRI positively correlated with microRNA-130b ($P<0.001$). Moreover, ARFI showed also a positive correlation with microRNA-130b ($P=0.029$). In NAFLD patients without CKD, ARFI positively correlated with microRNA-130b ($P=0.002$) (Fig. 1a–c).

Diagnostic performance of microRNA-130b

By ROC analysis, microRNA-130b showed a significant diagnostic performance in the discrimination between patients (groups I + II) from control cases. At a cutoff value > 27.55 copies/μl, microRNA-130b could achieve this differentiation with a sensitivity of 60%, and a specificity of 85%, and with positive predictive value (PPV) and negative predictive value (NPV) of 88.9% and 51.5%, respectively ($AUC=78.3\%$, $P<0.001$) (Fig. 2a). microRNA-130b showed a significant diagnostic performance in the discrimination between patients with "NAFLD with CKD" and patients with "NAFLD without CKD." At a cutoff value > 28.13 copies/μl, microRNA-130b could achieve this differentiation with a sensitivity of 75%, and a specificity of 70%, and with PPV and NPV of 71.4% and 73.7%, respectively ($AUC=71.9\%$, $P=0.018$) (Fig. 2b).

In addition, microRNA-130b has a significant diagnostic performance to discriminate between "NAFLD without CKD" patients from the control group. At a cutoff value > 24.81 copies/μl, microRNA-130b had a sensitivity, specificity, PPV, and NPV of 75%, 60%, 65.2%, and 70.6%, respectively ($AUC=70.6\%$, $P=0.026$) (Fig. 2c).

Discussion

Currently, NAFLD represents the upcoming epidemic of chronic liver disease worldwide after the elimination of the hepatitis C virus [1]. There is growing evidence that the synthesis and release of pro-inflammatory cytokines in NAFLD are connected to the development of CKD among NAFLD patients [7].

Recently, microRNAs have been linked to the manipulation of vital renal functions. The progression of renal illnesses such as DKD, acute kidney injury, lupus nephritis, and polycystic kidney disease has been linked to changes

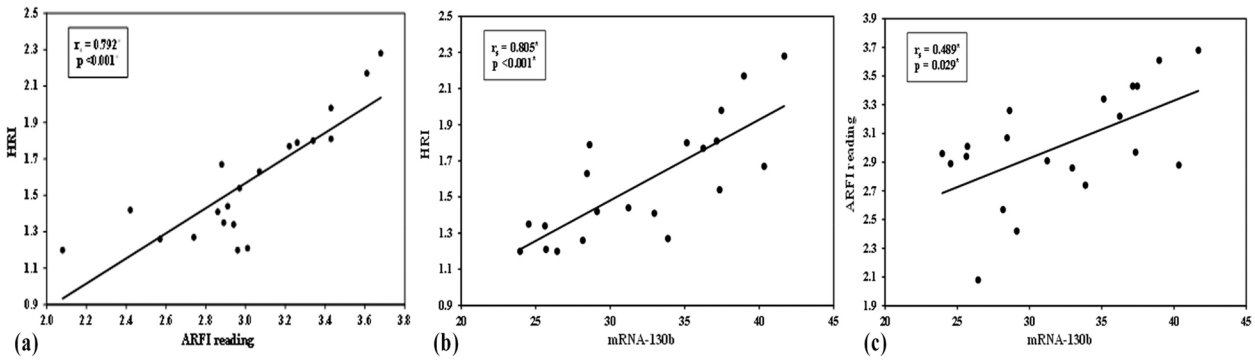

Fig. 1 Correlations in group I. **a** Between HRI and ARFI readings. **b** Between HRI and microRNA-130b. **c** Between ARFI reading and microRNA-130b

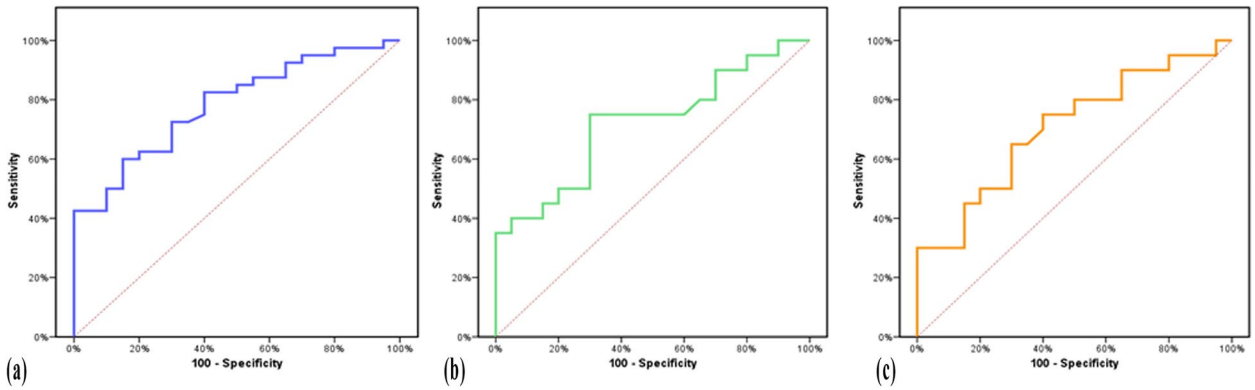

Fig. 2 Diagnostic performance and ROC analysis of microRNA-130b in discrimination of different study groups. **a** All patients vs. healthy control. **b** Nonalcoholic fatty liver disease associated with chronic kidney disease vs. nonalcoholic fatty liver disease but without chronic kidney disease. **c** Nonalcoholic fatty liver disease without chronic kidney disease vs. healthy control

in the expression of microRNAs. In addition, microRNAs have potential diagnostic and therapeutic targets [12, 13].

Our obtained results showed a significant difference between study groups as regards the HRI values. The same results apply to ARFI readings also. The hepatorenal index is considered a valid tool for detecting and grading fatty liver disorders in the previous report, and its utility for diagnosis and grading of liver steatosis has been studied. In addition, ARFI has been studied as a non-invasive tool for the assessment of liver steatosis in NAFLD [11, 17–20].

MicroRNA-130b is anticipated to be convoluted in pathophysiological procedures such as oxidative stress and insulin resistance which is the main underlying pathophysiological mechanism in NAFLD [12].

In our study, there microRNA-130b showed arithmetical variance in NAFLD patients with CKD than those without CKD ($P=0.032$), also showed arithmetical variance between NAFLD patients with CKD and control, and between NAFLD patients and control ($P<0.001$ and $P=0.045$) respectively.

MicroRNA-130b downregulation has been linked to a reduction of lipid storage in hepatocytes and improving insulin sensitivity in rat models. miR-130b-5p repression was found to decrease fat accumulation through insulin-like growth factor binding protein 2 (IGFBP2) upregulation in NAFLD murine models [21]. Growing evidence revealed that miR-130b is upregulated in a variety of diseases. For example, hepatocellular carcinoma tissues showed high expression of microRNA-130b compared to nearby cirrhotic nonmalignant liver tissues [22]. In addition, microRNA-130b has been linked to tumor cell initiation, growth, and apoptosis regulation [23]. These findings explain the higher levels of microRNA-130b among NAFLD patients compared to healthy control and represent a novel insight into the pathogenesis of NAFLD.

In our study, NAFLD patients with CKD had significantly higher levels of microRNA-130b compared to NAFLD without CKD and healthy subjects. In addition, microRNA-130b could discriminate patients with NAFLD and CKD from patients with NAFLD only with high sensitivity and specificity. This highlights the possible link and role of microRNA-130b in the development of CKD among NAFLD patients.

In recent years, a link between NAFLD and CKD has been established, irrespective of the existence of potential confounding disorders such as obesity, hypertension, and type 2 diabetes [24, 25].microRNA-130b has been linked to the development of CKD. Its level is upregulated in patients with early lupus nephritis and is positively correlated with renal damage and chronicity index. The increased expression of microRNA-130b has been associated with overexpression of α-smooth muscle actin and reduced expression of E-cadherin in the presence of transforming growth factor-β1 (TGFBR1). This was hypothesized to promote epithelial-mesenchymal transition, favoring renal tubular fibrosis [26, 27]. In addition, the link of miRNA-130 to TGFBR1 and TGFBR2 is of special importance as it may influence the fibrosis progression in NAFLD and may explain the pathogenesis of CKD in NAFLD patients, a point of potential therapeutic implication in the future [28].

On the other hand, contradictory data about the role of microRNA-130b in renal tubular function manipulation have been elucidated. Bai and colleagues (2016) found that microRNA-130b downregulation was associated with high serum creatinine and β2-microglobulin and with high Snail expression leading to increased tubulointerstitial fibrosis in diabetic nephropathy. However, this contradiction in results may be attributed to the presence of diabetes among their cohort. This concludes the role of microRNA-130b in the manipulation

of renal tubular function is not fully clear and opens the way for more studies [29].

We admit that our study has some limitations. The small sample size is one of these limitations, but the financial aspect of the higher number was a conflicting obstacle. We did not use liver biopsy in our diagnosis of NAFLD. This was due to its invasive nature and the resistance of NAFLD patients to such invasive maneuvers. *In conclusion*, the positive correlation between ARFI, HRI, and serum microRNA-130b, together with good diagnostic performance of microRNA-130b in discrimination of NAFLD patients with and without CKD, introduces these parameters as new non-invasive biomarkers for assessment of NAFLD and to predict chronic kidney disease, and we recommend further wide-scale evaluation of their utility in clinical practice.

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Authors' contributions
ME, study concept and design; ASE and MT, study concept; EEH, clinical examination and cases enrollment; ARFI, examination, data collection, and first draft; SAL, study design; ARFI, examination; and HRI, calculation and first draft. All the authors read and approved the final manuscript.

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Availability of data and materials
The authors confirm that the data supporting the findings of this study are available within the article.

Declarations

Ethics approval and consent to participate
This work was carried out following the Declaration of Helsinki for experiments 1975 and its later amendments. The study protocol was approved by the ethical committee of the Faculty of Medicine, Alexandria University, number 0201088. All patients signed a written informed consent before inclusion in the study.

Consent for publication
The authors declare that they consent to the publication of this study.

Competing interests
The authors declare that they have no competing interests.

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