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MiR-378a-3p AND miR-181b-5p AS NONALCOHOLIC STEATOHEPATITIS NON-INVASIVE DIAGNOSTIC BIOMARKERS AND THEIR CORRELATIONS WITH LIVER FIBROSIS

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Nonalcoholic steatohepatitis (NASH) is one of the most common liver diseases that is diagnosed by biopsy and, therefore, requires the development of non-invasive tests for diagnosis. Serum levels of microRNAs were shown to correlate with the severity of various liver diseases, but the role of miR-378a and miR-181b-5p in NASH remains unclear. The current study aims to assess the serum expression level of miR-378a-3p and miR-181b-5p in patients with NASH and to find out the correlation of these indices with liver fibrosis. The case-control research was carried out on 60 patients with confirmed NASH relative to 50 healthy subjects. Extraction and reverse transcription of micro RNAs was performed using miRCURY LNA RT Kit (Qiagen, Maryland, USA) Detection of miR-378a-3p and miR-181b-5p was done using qPCR. It was shown that serum expression level of miR-378a-3p in NASH patients was downregulated with a median range fold change 0.29, while that of miR-181b-5p was upregulated with a median range fold change 13.08. The ROC curve was constructed to discriminate the NASH group from the healthy group. The optimal cut-off value of miR-378a-3p was ≤0.031 with a sensitivity of 65%, the optimal cut-off value of miR-181b-5p was ≥ 0.063 with a sensitivity of 93.3%. Statistically significant positive correlation between miR-181b-5p level and fibroscan data was demonstrated. The present study showed that serum miR-378a-3p and miR-181b-5p could be used as biomarkers of NASH.

K e y w o r d s: nonalcoholic steatohepatitis (NASH), miR-378a-3p, miR-181b-5p, liver fibrosis.

Non-alcoholic steatohepatitis (NASH) is one of the most common liver diseases, which is characterized by hepatic swelling, ballooning, steatosis, as well as varying amounts of pericellular fibrosis [1]. It contributes to an increase in the incidence of hepatocellular carcinoma and cirrhosis globally, so it is considered a growing public health issue [2]. A liver biopsy is considered the gold standard method for diagnosis of NASH, but being an invasive procedure with many potential risks made it crucial to develop easily non-invasive tests for the diagnosis of NASH [3].

MicroRNAs (miRNAs) are single-stranded RNA strands of 20–25 nucleotides and do not code for any protein. Regulation of gene expression is one of the main functions of miRNAs [4].

Novel studies on the mechanism of development of NASH were stimulated by the discovery of miRNAs. Variations in miRNA expression have been documented in patients with NASH and hepatosteatosis [5]. Serum levels of microRNAs are correlated with disease severity in various liver diseases [6].

MiR-378a is an intronic miRNA placed in the *Ppargc1b* gene [7]. One of the family members of miR-181 is miR-181b-5p, which is considered a mature sequence of miR-181b [8]. MiR-378a and miR-181b-5p have been found to involve in vatious diseases, but their roles in NASH remain unclear [8].

The current study aimed to assess the expression levels of miR-378a-3p and miR-181b-5p in patients with NASH relative to healthy subjects. Also,

we aimed to demonstrate their correlations with fibroscan data and other clinical and laboratory parameters.

Materials and Methods

The current case-control research was carried out on 60 patients with ultrasound and fibroscan confirmed NASH. The inclusion criteria were: 1 - Patients aged 18 years or older. 2 - Findings of ultrasound and fibroscan that suggested the presence of steatohepatitis.

The patients were recruited from the outpatient clinic at the Department of Internal Medicine, Fayoum University Hospital, Fayoum. Former written and informed consent for each participant was given. The present research was approved by the Ethical Committee of the Faculty of Medicine, Fayoum University in accordance with the Declaration of Helsinki and compliance with Ethical Standards.

Ethical approval and consent to participate. Written and informed consent was obtained from each participant. The present research was approved by the Ethical Committee of the Faculty of Medicine, Fayoum University (Code No. EC 2379) in accordance with the Declaration of Helsinki and compliance with Ethical Standards.

Consent for publication. Patients and the control group provided written informed consent. Patients participating in this study consent to data publication.

The excluded patients from this study were: 1 - patients with other types of hepatic diseases; 2 - patients with autoimmune diseases or malignancy; 3 - patients with other severe systemic diseases; 4 - patients who had consumed alcohol.

In addition, 50 control individuals with normal liver enzymes and normal abdominal ultrasonography and without a history of any hepatic diseases for at least six months prior to the study were involved.

Full history (personal and medical) was fulfilled from each participant. Furthermore, routine laboratory tests were performed. Liver stiffness was assessed by Fibroscan.

Preparation of blood samples. A Vacutainer system containing a gel separator was used to withdraw 3ml peripheral venous blood samples from each participant. The tubes were left to clot for 15 min at room temperature after which they were centrifuged at 3000 rpm for 10 min. Serum samples were separated and stored at -80°C pending the time of microRNA extraction.

Extraction and reverse transcription of microRNAs. Purification of serum whole RNA, including microRNA, was done via miRNeasy mini kit (Qiagen, Valencia, CA, USA) in agreement with the manufacturer's instructions.

NanoDrop® (ND)-1000 spectrophotometer (NanoDrop Technologies, Inc. Wilmington, USA) was used to measure RNA quantitation and purity.

Reverse transcription of the extracted RNA was performed using miRCURY LNA RT Kit (Qiagen, Maryland, USA) in a total volume of 10 ul RT reactions in line with the instructions of the manufacturer's protocol.

Detection of miR-378a-3p and miR-181b-5p via using quantitative real-time PCR (qPCR). The reagents of miRCURY LNA SYBR® Green Master Mix [Qiagen, Maryland, USA] and miRCURY LNA miRNA PCR Assays [Qiagen, Maryland, USA] as well as synthesized cDNA were used to form PCR reaction mix for a 10 µl for each reaction.

The real-time cycler (Thermo Scientific™, PikoReal 24™ Real-Time PCR System, Finland) was planned as follows: initial heat activation at 95°C for 2 min, subsequently, denaturation (40 cycles) at 95°C for 10 s, combined annealing/extension at 56°C for 60 s. Melting curve analysis at 60-95°C was performed to determine the specificity of the amplified products. The samples yielded only one peak, indicating the high specificity of the reactions in the current study (amplification of primer dimers yielded another peak at a lower temperature).

Expression levels of miR-378a-3p and miR-181b-5p were evaluated with miR-16-5p as internal control [9-11] using primers for miR-378a-3p and miR-181b-5p and miR-16-5p that were ready-made. Catalog no. of miR-378a-3p was YP00205946.

And its Lot number was 201803080066-6, Catalog no. of miR-181b-5p was YP00204530 and its Lot number was 201803060203-2, Catalog no. of miR-16-5p was YP00205702 and its Lot number is 201910040131-3.

Gene expression relative to internal control ($2^{-\Delta Ct}$) was assessed. Fold change (FC) was considered using $2^{-\Delta\Delta Ct}$ for each patient.

MiRNA was upregulated if the FC value was above 1, though miRNA was downregulated if the FC value was less than 1. The values of controls were set equal to 1 because $-\Delta\Delta Ct$ for control subjects equals zero [11].

Statistical methods. Statistical Package for Social Sciences (SPSS) version 18 was used to prepare the current data statistically. For analyzing

quantitative data, the median, interquartile range (IQR), mean and standard deviation (SD) were applied. For qualitative data (presented as numbers and percentages), a chi-square test was performed. The correlation of miR-378a-3p and miR-181b-5p with clinical, laboratory, and fibroscan data was evaluated using Spearman's correlation. To recognize the cut-off point, sensitivity, and specificity of miR-

Table 1. Demographic and clinical characteristics among study groups

Parameters		Cases (n = 60)	Control (n = 50)
Sex (male : female)	n (%)	34(56.7%) : 26(34.3%)	32(64%) : 18(36%)
Age (years)	Mean ±SD	39.68 ± 1.09	38.16 ± 9.90
BMI (kg/m^2)	Mean ±SD	33.32 ± 7.063	
Waist circumference (cm)	Mean ±SD	105.05 ± 30.05	
Laboratory data			
AST (IU/l)	Mean ± SD	20.25 ± 5.047	
ALT (IU/l)	Mean ± SD	21.90 ± 15.826	
γGT (IU/l)	Mean ± SD	24.88 ± 12.986	
Bilirubin (mg/dl)	Mean ± SD	0.378 ± 0.167	
Albumin (g/dl)	Mean ± SD	4.700 ± 0.257	
Fasting blood sugar (mg/dl)	Median(IQR)	93(88-160)	
HOMA IR	Median(IQR)	2.57(1.59-4.060)	
HbA1c (%)	Mean ± SD	5.90 ± 1.77	
Fasting insulin (μU/ml)	Median(IQR)	11.7(7.5-13.9)	
Total cholesterol (mg/dl)	Mean ± SD	213.53 ± 41.56	
HDL (mg/dl)	Mean ± SD	45.83 ± 11.80	
LDL (mg/dl)	Mean ± SD	133.58 ± 32.639	
Triglyceride (mg/dl)	Median(IQR)	110(75-219)	
VLDL (mg/dl)	Median(IQR)	22(15-43.8)	
T.ch/HDL	Mean ± SD	5.05 ± 1.78	
LDL/HDL	Mean ± SD	3.15 ± 1.216	
TSH (mIU/l)	Mean ± SD	1.73 ± 0.72	
FT3 (ng/dl)	Mean ± SD	3.32 ± 0.43	
FT4 (ng/dl)	Mean ± SD	1.28 ± 0.17	
Sonar data			
LSFT (cm)	Mean ± SD	2.59 ± 0.98	
USFT (cm)	Mean ± SD	4.53 ± 2.12	
PV diameter (mm)	Median(IQR)	1(0.83-1.1)	
Spleen (cm)	Mean ± SD	10.11 ± 1.625	
Fibro scan data			
Fibroscan	Median(IQR)	5.75 ± 4.149	
Controlled attenuation parameter	Median(IQR)	251.93 ± 128.01	

Note. AST – Aspartate transaminase, ALT – alanine transaminase, γGt – gamma glutamyltransferase, HOMA IR – homeostatic model assessment for insulin resistance, HbA1c – glycated hemoglobin, HDL – high-density lipoprotein, LDL – low-density lipoprotein, VLDL – very low-density lipoprotein, T.ch – total cholesterol, TSH – thyroid-stimulating hormone, FT3 – free thyroxine 3, FT4 – free thyroxine 4, LSFT – midline abdominal subcutaneous fat thickness in front of the liver, USFT – paraumbilical abdominal subcutaneous fat thickness, PV – portal vein

378a-3p and miR-181b-5p as biomarkers for NASH, a receiver operating characteristic (ROC) curve was constructed. Significance was considered at $P \leq 0.05$.

Results

Demographic and clinical parameters. Demographic and clinical data of NASH patients and controls are shown in Table 1. There was no significant variation regarding age and sex between both groups ($P = 0.445$, $P = 0.434$), respectively.

Serum expression levels of miR-378a-3p and miR-181b-5p in NASH cases and control subjects. The relative expression level of miR-378a-3p was reduced, with median range fold change (intraquartile range) = 0.29 (0.12-1.32), $P = 0.002$. However, the serum expression level of miR-181b-5p was elevated, with median range fold change (intraquartile range) =13.08(5.34-37.21), $P < 0.001$, Fig. 1.

Diagnostic performance of miR-378a-3p and miR-181b-5p in NASH. The ROC curve was constructed to discriminate the NASH group from the control group. As a result, the cut-off point of miR-378a-3p was ≤0.031 with a sensitivity of 65%, a specificity of 65.5%, $P = 0.029$, and an area under the curve (AUC) (95% confidence interval) 0.643(0.52-0.77). The optimal cut-off value of miR-181b-5p was ≥ 0.063 with a sensitivity of 93.3%, a specificity of 82.4%, $P < 0.001$, and AUC (95% confidence interval) 0.88(0.785-0.970) (Table 2 and Fig. 2).

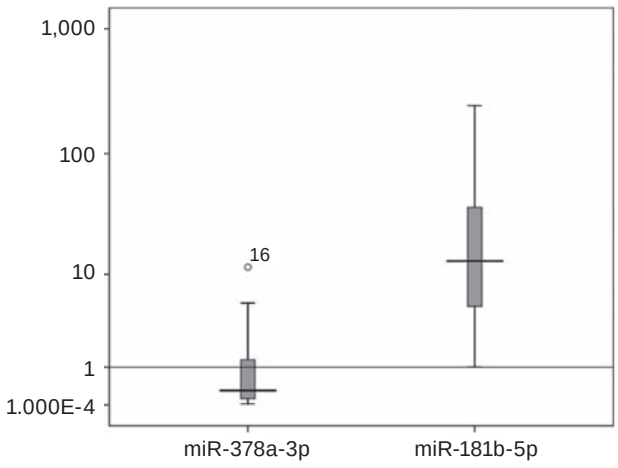

Fig. 1. Box plot representation of serum expression of miR-378a-3p and miR-181b-5p level in NASH cases and control subjects. The ends of the box are the upper and lower quartiles. The horizontal line inside the box represents the median value. The two lines outside the box mark the highest and lowest values. Data on the far upper or lower side are outliers (as 16). Control Fold-change values of miR-378a-3p and miR-181b-5p were represented by the horizontal line (were set as 1)

Correlation of miR-378a-3p and miR-181b-5p serum expression levels with demographic, laboratory, and clinical data of NASH cases. As illustrated in Table 3, there was a statistically significant positive correlation between miR-378a-3p and height ($r = 0.297$; $P = 0.021$). A significant positive correlation between miR-181b-5p and weight ($r = 0.289$; $P = 0.025$) was also noted. Furthermore, there was a statistically significant positive correlation between miR-378a-3p and each of triglyceride ($r = 0.320$; $P = 0.013$), very low-density lipoprotein (VLDL) ($r = 0.320$; $P = 0.013$) as well as thyroid-stimulating hormone (TSH) ($r = 0.285$; $P = 0.027$).

Correlations between miR -378a-3p,miR-181b-5p, and each of abdominal sonar and fibroscan data among NASH group. As shown in Table 4, there was a statistically significant positive correlation between miR-181b-5p and pelvic vein (PV) diameter ($r = 0.362$; $P = 0.004$).

Moreover, Table 5 illustrates that there were statistically significant positive correlations between miR-181b-5p and each of fibroscan (F) ($r = 0.291$; $P = 0.028$) and controlled attenuation parameter (CAP) ($r = 0.271$; $P = 0.036$).

Discussion

The prevalence of non-alcoholic fatty liver disease (NAFLD) is growing [1]. The prognosis of NAFLD is commonly benign. However, numerous patients progress to non-alcoholic steatohepatitis (NASH), which might develop cirrhosis and hepatocellular carcinoma (HCC) [12, 13].

The number of miRNAs, about 2000, targets 30–60% of the human genes [14]. Moreover, several studies have reported the function of miRNAs in lipid metabolism, tissue development, and apoptosis in the liver. Interestingly, dysregulation of miRNAs has been documented in different diseases, including NAFL, NASH, and HCC [4, 15, 16].

Circulating miRNAs have been estimated as non-invasive diagnostic biomarkers for investigating many pathological conditions due to their stability and the inability of ribonucleases to degrade them [17]. They are used for early discovery and revealing illness progression. In recent work, miRNAs might be considered as non-invasive biomarkers for NASH [18].

Table 2. Evaluation of the role of serum levels of miR378a-3p and miR-181b-5p in distinguishing NASH cases from healthy subjects

Parameters	Cut off point	AUC(95% CI)	Sensitivity	Specificity	*P* value
miR-378a-3p	≤0.031	0.643(0.52-0.77)	65%	65.5%	0.029*
miR-181b-5p	≥0.063	0.88(0.785-0.970)	93.3%	82.4%	<0.001*

Note. AUC – Area under the curve, CI – confidence interval. *Significant $P < 0.05$

In the present study, we observed that the relative expression levels of miR-378a-3p were decreased, with median range fold change (intraquartile range) = 0.29 (0.12-1.32), $P = 0.002$ in patients with NASH relative to healthy subjects.

Our results resemble previous studies, which verified that the expression of miR-378a-3p is reduced throughout hepatic fibrosis [19].

Further studies revealed that miR-378a was declined in cirrhotic patients relative to healthy individuals [20].

Also, the reduced expression level of miR-378a was related to methylation of the promoter in transforming growth factor-β1 (TGF-β1)-treated liver stellate cells (HSCs), which proposes an inhibitory function of miR-378a in hepatic fibrosis [21].

Similarly, Zaafan and Abdelhamid observed that miR-378a expression noticeably declined in hepatic tissues, which are fibrosis [22].

Our results are not in accordance with Zhang et al. who found that hepatosteatosis vigorously stimulates the transcription of miR-378 [23]. Besides, accumulating data verified that miR-378 has a role in insulin resistance and hepatosteatosis [24].

In the current research, the level of miR-181b-5p is over-expressed, with median range fold change (intraquartile range) =13.08(5.34-37.21), $P < 0.001$.

The latest data verified a marked increase in the level of miR-181b in patients with NASH [25], indicating that the abovementioned microRNA has a vital role in hepatic injury and tumor progress. In another work, Meng et al. showed that miR-181a and miR-181b were increased in hepatocellular cancer stem cell (CSC) populations, demonstrating that miR-181 might have a role in treating HCC patients through maintaining an undifferentiated state of CSCs [26].

Interestingly, Wang et al. found that the serum levels of miR-181b were extensively enhanced in the patients with NAFLD compared with the healthy individuals ($P < 0.01$) and upregulated miR-181b in NAFLD targets SIRT1. Moreover, *in vivo* and *in vitro* suppression of miR-181b in the induced NAFLD model confirmed the possibility of using miR-181b in the treatment of NAFLD. Their study reported

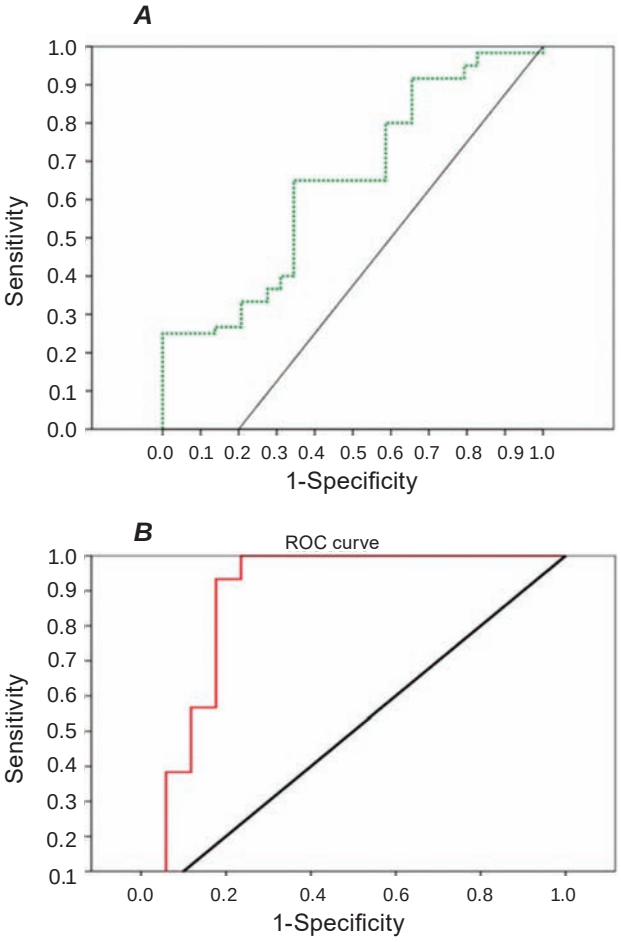

Fig. 2. The receiver-operating characteristic (ROC) curve of miR-378a-3 and miR-181b-5p explains their role in differentiating NASH cases from controls. ***A*** *– The optimal cut-off value of miR-378a-3p was ≤0.031 with a sensitivity of 65%, a specificity of 65.5%, P = 0.029, and AUC (95% CI) 0.643(0.52-0.77).* ***B*** *– The optimal cut-off value of miR-181b-5p was ≥0.063 with a sensitivity of 93.3%, a specificity of 82.4%, P < 0.001, and AUC (95% CI) 0.88(0.785-0.970)*

Table 3. Correlations between miR-378a-3p, miR-181b-5p, and demographic and clinical variables amongthe NASH group

Parameters	miR-378a-3p		miR-181-5p	
	r	*P* value	*r*	*P* value
Age (years)	-0.029	0.824	-0.146	0.267
Weight (kg)	0.008	0.950	**0.289***	**0.025**
Height (cm)	**0.297***	**0.021**	0.246	0.058
BMI (kg/m^2)	0.076	0.714	0.107	0.424
Waist circumference (cm)	-0.059	0.655	0.161	0.223
AST (IU/l)	0.128	0.336	0.010	0.940
ALT (IU/l)	0.163	0.217	0.099	0.455
γGT (IU/l)	0.049	0.713	0.212	0.106
Bilirubin (mg/dl)	-0.088	0.506	0.103	0.437
Albumin (g/dl)	0.071	0.595	-0.175	0.184
Fasting blood sugar (mg/dl)	0.092	0.490	0.063	0.635
HOMA IR	0.074	0.579	-0.084	0.528
HbA1c (%)	-0.142	0.283	-0.105	0.428
Fasting insulin (μU/ml)	0.125	0.340	-0.023	0.864
Total cholesterol (mg/dl)	0.218	0.096	0.045	0.734
HDL (mg/dl)	-0.086	0.517	-0.111	0.403
LDL (mg/dl)	0.111	0.401	-0.008	0.954
Triglyceride (mg/dl)	**0.320***	**0.013**	0.241	0.066
VLDL (mg/dl)	**0.320***	**0.013**	0.241	0.066
T.ch/HDL	0.249	0.058	0.092	0.490
LDL/HDL	0.152	0.251	-0.011	0.936
TSH (mIU/l)	**0.285***	**0.027**	0.150	0.251
FT3 (ng/dl)	0.181	0.166	-0.052	0.695
FT4 (ng/dl)	-0.223	0.089	-0.148	0.263

Note. NASH – nonalcoholic steatohepatitis, AST – aspartate transaminase, ALT – alanine transaminase, γGt – Gamma glutamyltransferase, HOMA IR – homeostatic model assessment for insulin resistance, HbA1c – glycated hemoglobin, HDL – high-density lipoprotein, LDL – low-density lipoprotein, VLDL – very low-density lipoprotein, T.ch – total cholesterol, TSH – thyroid-stimulating hormone, FT3 – free thyroxine 3, FT4 – free thyroxine 4. *Significant $P < 0.05$

that miR-181b is elevated while SIRT1 is suppressed in the serum of NAFLD patients. Also, miR-181b targets SIRT1 expression that could regulate liver steatosis. Their work demonstrated that miR-181b could be a new therapeutic target for NAFLD [27].

Similarly, the Wang et al. study proved that the serum level of miR-181b-5p was upregulated in alcohol-related fatty liver disease (AFLD) rat liver tissues, miR-181b-5p suppression could improve hepatic function, decreased oxidative stress inflammation, oxidative stress, hepatocyte apoptosis as well as pathological changes in AFLD rat liver tissues [28]. In another study, fibrotic tissue showed increased miR-181b expression that could have a role in liver fibrogenesis. MiR-181b might regulate the activation of hepatic stellate cells (HSCs), at least in part, via phosphatase and tensin homolog deleted on chromosome 10 (PTEN)/Akt pathway [29]. Furthermore, preceding data reported that serum miR-181b levels were markedly enhanced in patients with cirrhosis [30]. This result showed that miR-181b could be a possible diagnostic serum marker for hepatic cirrhosis.

Table 4. Correlations between miR -378a-3p,miR-181b-5p, and abdominal sonar data among the NASH group

Parameters	miR-378a-3p		miR-181-5p	
	r	*P* value	*r*	*P* value
Right hepatic lobe (cm)	0.079	0.554	0.235	0.076
Grade of steatosis	0.058	0.667	0.175	0.188
LSFT (cm)	-0.095	0.480	0.111	0.405
USFT (cm)	0.017	0.895	0.235	0.071
PV diameter (mm)	0.164	0.211	0.362*	0.004
Spleen (cm)	0.071	0.598	0.151	0.257

Note. NASH – Nonalcoholic steatohepatitis, LSFT – midline abdominal subcutaneous fat thickness in front of the liver, USFT – paraumbilical abdominal subcutaneous fat thickness, PV – portal vein. *Significant $P < 0.05$

Table 5. Correlations between miR-378a-3p,miR-181b-5p, and fibroscan data among the NASH group

Parameters	miR-378a-3p		miR-181b-5p	
	r	*P* value	*r*	*P* value
Fibroscan	0.102	0.450	0.291*	0.028
Controlled attenuation parameter	0.118	0.368	0.271*	0.036

Note. NASH – Nonalcoholic steatohepatitis. *Significant $P < 0.05$

Wang et al. 2009 study indicated a direct role of transforming growth factor-beta (TGFb) throughout NASH-associated hepatocarcinogenesis via regulating the expression of miR-181 [31].

Also, It was reported in a previous study that members of the miR-181 family are overexpressed in liver stem cells and HCC cells [32].

In the current study, in terms of diagnostic efficacy for NASH, mir-378a-3p shows moderate accuracy with a specificity of 65.5%, and its sensitivity is low at 65%.The cut-off point of miR-181b-5p was ≥0.063 with a sensitivity of 93.3%, a specificity of 82.4%, $P < 0.001$ and AUC 0.88(0.785-0.970).

To sum up, the present study showed that serum miR-378a-3p and miR-181b-5p could be used as biomarkers of NASH and perhaps act as potential therapeutic targets. Also, there were statistically significant positive correlations between miR-181b-5p and each of F and CAP, indicating its correlation with liver fibrosis.

It is important to address some of this work's limitations. The first is the tiny sample size. Therefore, additional research using bigger sample sizes in different populations is required.

Additional prospective studies should be conducted to understand better the mechanisms of action and how these non-coding RNAs function in NASH patients.

Conflict of interest. The authors have completed the Unified Conflicts of Interest form at http://ukrbiochemjournal.org/wp-content/uploads/2018/12/coi_disclosure.pdf and declare no conflict of interest.

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Availability of data and materials. The article contains the information utilized to support the conclusions of this study.

MIR-378A-3P ТА MIR-181B-5P ЯК НЕІНВАЗИВНІ ДІАГНОСТИЧНІ БІОМАРКЕРИ НЕАЛКОГОЛЬНОГО СТЕАТОГЕПАТИТУ ТА ЇХ КОРЕЛЯЦІЯ З ФІБРОЗОМ ПЕЧІНКИ

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Неалкогольний стеатогепатит (НАСГ) - одне з найпоширеніших захворювань печінки, яке діагностується за допомогою біопсії і тому потребує розробки неінвазивних тестів для діагностики. Було показано, що рівень мікроРНК у сироватці крові корелює з тяжкістю різних захворювань печінки, але роль miR-378a та miR-181b-5p у НАСГ залишається нез'ясованою. У дослідженні оцінювали рівень експресії miR-378a-3p та miR-181b-5p у сироватці крові пацієнтів з НАСГ та кореляцію цих показників із фіброзом печінки. У дослідженні "випадок-контроль" брали участь 60 пацієнтів із НАСГ у порівнянні з 50 здоровими особами. Екстракцію та зворотню транскрипцію мікроРНК проводили за допомогою miRCURY LNA RT Kit (Qiagen, Меріленд, США). Визначення miR-378a-3p та miR-181b-5p здійснювали за допомогою qPCR. Показано, що рівень експресії miR-378a-3p у сироватці крові пацієнтів з НАСГ був знижений з кратністю зміни медіани розмаху 0,29, тоді як рівень експресії miR-181b-5p був підвищений з кратністю зміни медіани розмаху 13,08. ROC-крива була побудована для того, щоб розрізнити групу НАСГ та групу здорових людей. Оптимальне порогове значення для miR-378a-3p становило ≤0,031 з чутливістю 65%, оптимальне порогове значення для miR-181b-5p становило ≥0,063 з чутливістю 93,3%. Була продемонстрована статистично значуща позитивна кореляція між рівнем miR-181b-5p та даними фіброскану. Отримані результати показали, що miR-378a-3p та miR-181b-5p в сироватці крові можуть бути використані як біомаркери НАСГ.

Ключові слова: неалкогольний стеатогепатит, miR-378a-3p, miR-181b-5p, фіброз печінки.

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