



Original Article

Expression of MicroRNA-155-5p in Chronic Kidney Disease as a Potential Marker of Cardiovascular Complications

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ABSTRACT

Background: Chronic kidney disease (CKD) is a silent, serious condition requiring reliable non-invasive markers for diagnosing and predicting complications especially cardiovascular (CV) complications.

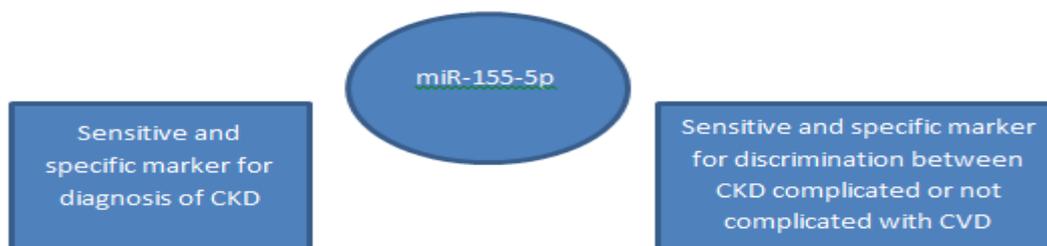
Objectives: This study aims to detect microRNA-155-5p (miR-155-5p) as a potential marker of CKD and a predictor of CV complications.

Subjects and methods: 120 participants were included in this study, and they were categorized as; Group I (n=60, healthy age- and sex-matched control group) and Group II (n = 60, CKD patients). Group II was subdivided into: Group IIA (n = 30 CKD patients without CV complications) and Group IIB (n = 30; CKD patients complicated with CV diseases). Using reverse transcription polymerase chain reaction (RT-PCR), miR-155-5p was detected.

Results: miR-155-5p was increased in Group IIA and IIB compared with the control group, while miR-155-5p was increased in Group IIB compared with Group IIA.

Conclusion: miR-155-5p can be used as a sensitive and specific marker for detecting CKD and discriminating between CKD with and without CV complications.

GRAPHICAL ABSTRACT



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Introduction

Chronic kidney disease (CKD) is a global disease because of its high incidence, high prevalence, insidiousness, poor prognosis, and numerous severe complications [1]. It is a major problem in Egypt as it is the 5th leading cause of death from 2009 to 2019 [2].

It continues to be a health-care burden worldwide with deleterious health consequences, including cardiovascular diseases (CVD) [3].

Currently, CKD is mainly diagnosed via biological marker detection such as urea, creatinine and estimated glomerular filtration rate (eGFR), ultrasound imaging, and kidney biopsy. Due to radioactive and traumatic concerns, the radionuclide method and renal biopsy are difficult for routine use. Furthermore, creatinine and ultrasound imaging has some limitations in assessing renal injury due to their low sensitivity [4]. Therefore, new biomarkers and methods are essential to improve diagnostic efficiency in CKD. Small non-coding RNA fragments called microRNAs (miRs) that are, on average, 22 nucleotides in length play a significant part in post-transcriptional gene regulation [5]. In addition to their role in diagnosis, they aid in prognosis and treatment decisions for physicians. Moreover, they could also be used as therapeutic targets [6].

Although the relevance of miRs in many instances is still obscure, some miRs have been suggested to have a role in CKD [7]. The miRs function in different renal diseases were explored, including acute renal injury, glomerulonephritis, or systemic autoimmune disorders [8-12].

The gene for microRNA-155 (miR-155), located on the third exon of the B cell integration cluster gene on chromosome 21q21, is highly abundant in the thymus and spleen, and is found in the liver, lungs, and kidneys [13]. It becomes increasingly obvious that miR-155 has an important role in the pathogenesis of kidney diseases. Although many studies revealed increased expression of the marker in acute kidney injury, its exact role in the pathogenesis of kidney diseases still not clear [14].

So, this study aimed to evaluate the miR-155-5p expression in the sera of people with chronic

kidney disease and its relation to eGFR. Furthermore, the potential of miR-155-5p as a discriminating factor between CKD and CKD complicated with CVD.

Materials and Methods

This case-control study was carried out on 120 participants selected from the outpatient clinic of the Nephrology Department of the National Institute of Urology and Nephrology, Cairo, Egypt. Cases were divided into two groups: Group I; (n = 60), that consisted of age and sex-matched healthy controls, Group II (n = 60), that consisted of chronic kidney disease (CKD) patients. Group II was subdivided into Group IIA (n = 30), CKD patients without cardiovascular complications, and Group IIB (n = 30), the CKD patients complicated with CVD.

Inclusion criteria

Following the 2012 Kidney Disease Improving Global Outcomes (KDIGO) recommendations for the assessment and treatment of CKD, eGFR categories G2-G5 (i.e., eGFR <90 mL/min/1.73 m²) were used to diagnose CKD patients.

Cardiovascular complications were detected using electro-cardiography (ECG) and cardiac markers such as cardiac troponin and creatine kinase-MB (CK-MB). Table 1 illustrates the stages and different pathologies of CKD patients.

Exclusion criteria

Patients with autoimmune disorders, malignancies, infections, smokers, and alcoholics were excluded from this study.

Ethical consideration

The study followed the World Medical Association Helsinki declaration guidelines for human participants in research. The Institutional Review Board of Al-Azhar University approved this study, and participants gave their written informed consent.

Procedures and assessment

All participants were subjected to a thorough history-taking and clinical evaluation with the following examinations:

- a. Routine laboratory investigations: Renal function tests, cardiac enzymes (creatinine kinase (CK), the isoenzyme (CK-MB), and lactate dehydrogenase (LDH) were performed using the automated chemistry analyzer Cobas c311 (Roche, Germany). Serum cardiac troponin was detected using the automated chemistry analyzer Cobas e411 (Roche, Germany).
- b. eGFR was calculated using the EPI formula [15].
- c. Plasma miR-155-5p was detected by RT-PCR:

The miRNeasy Mini Kit (cat. no. 217004, QIAGEN, Germany) was employed to extract RNA from plasma samples, and the miScript II RT Kit (cat. no. 218161, QIAGEN, Germany) was used to perform reverse transcription as per the manufacturer’s directions.

The miR-155-5p was quantified with a PCR ViiATM 7 System (Lot No. 278880908, USA)

employing human miscript SYBR green Master Mix, the primers for miR-155-5p (Cat. No. 218300, Lot No. 201907050022) and SNORD 68 (serve as the endogenous control) (Cat. No. MS00033712, Lot No. 201601113022s, QIAGEN, Germany)

The following cycling parameters were used: The first active stage of the PCR was at 95 °C for 15 minutes, followed by 40 cycles of denaturation at 94 °C for 15 seconds, annealing at 55 °C for 30 seconds, and extension at 70 °C for 30 seconds. To ensure specificity in the amplification, melting curve analysis was carried out after the thermal profile. The temperature increased very slowly (from 65-95 °C) while monitoring the fluorescence signal. Melting curve analysis resulted a single sharp peak for each target.

Fold-change values >1 indicate an up-regulation, and the fold-regulation equals to the fold-change. Fold-change values<1 indicate down-regulation, and the fold-regulation is the negative inverse of the fold-change. The values of both fold-regulation and fold-change are identical in this study as the miR-155-5p is upregulated.

Table 1: Staging and various pathologies of CKD patients

		Group II (chronic kidney disease patients) (n=60)	
		Count	%
The CKD stage	Stage 2	6	10%
	Stage 3	8	13.3%
	Stage 4	19	31.7%
	Stage 5	27	45.0%
The CKD Pathogenesis	Hypertension	15	25%
	Diabetes mellitus	10	16.7%
	Analgesic nephropathy	9	15%
	Pyelonephritis	7	11.7%
	Allergic interstitial nephritis	5	8.3%
	Glomerulonephritis	4	6.7%
	Membranous nephropathy	3	5%
	Obstructive uropathy	2	3.3%
	Interstitial nephritis	1	1.7%
	Medium sized vessels nephrosclerosis	1	1.7%
	Polycystic kidney disease	1	1.7%
	Eclampsia	1	1.7%
	Preeclampsia	1	1.7%

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 28 (IBM Corp., Armonk, NY, USA). Data were summarized using the mean and standard deviation or median, interquartile range, frequencies and percentages for normally distributed quantitative variables and non-normally distributed quantitative variables for categorical variables, respectively. When comparing the normally distributed quantitative data, unpaired t- tests or analysis of variance (ANOVA) with multiple comparisons post hoc tests were employed. In contrast, non-parametric Kruskal-Wallis and Mann-Whitney tests were employed for non-normally distributed quantitative data. The exact test was employed when the anticipated frequency was less than 5, whereas the Chi square (χ^2) test was employed to compare the categorical data. The Spearman correlation coefficient was used for correlation among quantitative variables. The best cutoff value of miR155-5p for case detection was discovered using a ROC curve and an area under the curve analysis. The statistical significance was determined using p-values ($p < 0.05$).

Results and Discussion

In total, 120 individuals were enrolled in the study, and they were divided into 2 categories: 60 volunteered healthy subjects (20 males and 40 females) as controls, between the age of 33-59 years old (45.97 ± 8.29) and 60 CKD patients who were further divided into two subgroups based on their eGFR and disease stage: Group IIA consisted of 30 CKD patients without CVD (9 males and 21 females), between the age of 32-71 years old (51.73 ± 14.02); Group IIB consisted of 30 CKD patients complicated with CVD (17 males and 13 females) between the age of 35-73 years old (60.77 ± 13.12).

The analysis of biochemical parameters for estimating the kidney and cardiac functions and eGFR showed significant differences ($p < 0.001$) among CKD patients, either complicated with or without CVD, compared with the control group (Table 2). However, non-significant differences were observed between the patient subgroups

except for the serum levels of total CK and CK-MB, which revealed a significant elevation ($p < 0.001$) in the complicated subgroup compared with the non-complicated one. Similarly, troponin was present in 50% of the serum samples in the complicated subgroup.

The median levels of miR-155-5p were significantly increased ($p < 0.001$) in the CKD patients compared with the control group. In addition, the miR-155-5p level of the subgroup IIB (CKD complicated with CVD) was significantly elevated ($p < 0.001$), compared to non-complicated subgroup IIA as recorded in Table 3. In CKD patients, there was no significant correlation between miR-155-5p and any of the biochemical parameters, eGFR, or the CKD stage, except a positive correlation between miR-155-5p and CK ($r = 0.647$, $p < 0.001$).

Circulating miRNAs are interesting non-invasive biomarkers because of their stability in plasma, serum, and urine. MiR-155-5p is a typical multifunctional miRNA and is widely expressed in different tissues playing critical roles in physiological and pathological processes [16]. Many studies have concluded that miR-155 plays a key role in inflammation, immune response, and hematopoiesis [17]. Serum miR-155 has been identified as a novel marker for the early detection and treatment of inflammation in patients with uremic dialysis [18].

Additionally, miR-155-5p is overexpressed in renal tissues and urine samples in many diseases including bladder cancer, IgA nephropathy, acute kidney injury (AKI), diabetic kidney disease (DKD), in renal tubular cells in diabetic nephropathy, and end-stage renal disease. It was upregulated in proximal tubular cell fibrosis *in vitro*, suggesting that it may contribute to the pathogenesis of renal fibrosis [19-25].

Regarding the miR-155-5p expression in plasma or serum samples, few studies discussed its relationship with either CKD or CVD. The findings of the current study were in concordance with Brigant *et al.* (2017). They reported that the miR-155 level is significantly upregulated in patients with CKD (stage III-V) and was not correlated with eGFR [26].

In agreement with the present study, Klimczak *et al.* (2017) showed that the miR-155-5p was elevated among CKD patients, and patients suffering from nocturnal hypertension had higher levels than the CKD patients. They recommended further studies to assess the miR-155 role as a unique diagnostic biomarker and a target for therapy in CKD patients with increased cardiovascular risk [27].

Matsumoto *et al.* (2012) found that miR-155 was upregulated in the sera of individuals with a greater chance of cardiac mortality. As a result, miR-155 may serve as a predictive indicator for cardiac mortality in patients after myocardial infarction [28].

Ikitimur *et al.* (2015) and Marques *et al.* (2016) showed that miR-155 was upregulated and positively correlated with left ventricular mass index, implying its use as a prognostic marker in heart failure patients [29, 30].

The ROC curve analysis determined the diagnostic efficacy with a cut-off point set as >1.835-fold change for miR-155-5p to distinguish between control and CKD patients. The AUC was 0.941, and the sensitivity and specificity were

91.7% and 93.3%, respectively (Figure 1). The ROC curve output data for the discrimination power of miR-155-5p to differentiate between the studied groups is shown in Table 4. The cutoff value became 1.834, the specificity and sensitivity of miR-155-5p became 93.3% and 83.3%, respectively, to discriminate between CKD patients without CVD and the control group, and the cutoff value became 5.214. The specificity and sensitivity of miR-155-5p reached 100% to discriminate between CKD patients with CVD and the control group, and the cutoff value was >14.55. The specificity and sensitivity of miR-155-5p were 93.3% and 90%, respectively, to discriminate between CKD patients without CVD and CKD complicated with CVD.

Regarding the discriminative power of miR-155-5p, this miR is a sensitive and specific marker for differentiation between CKD and healthy controls and between CKD with and without CVD complications. This suggests that miR-155-5p can be considered a minimally invasive diagnostic marker for CKD and a discriminating factor between CKD patients with and without CV complications.

Table 2: Statistical significance of serum parameters for kidney function (urea, creatinine, and uric acid), cardiac parameters (total CK, CK-MB, troponin, and LDH) and eGFR in the studied groups

Groups Parameters	Group I (n=60)	Group IIA (n=30)	Group IIB (n=30)
Urea (mg/dL) (Median, IQR)	27 (20-31)	93.95* (57.8-148)	86.5# (67.5-108)
Creatinine (mg/dL) (Median, IQR)	0.9 (0.8- 0.9)	3.1* (1.7-5.2)	3.85# (2.9-6.5)
Uric acid (mg/dL) (Median, IQR)	4.1 (3.5- 5)	7.15* (4.8- 9.6)	7.2# (5.4-9)
eGFR (ml/min.) (Median, IQR)	101.5 (94.1-109)	21* (12- 38)	13.5# (8.8-26)
CK (IU/L) (Mean± SD)	93.77 ± 29.82	123.67± 48.41*	289.1 ± 39.11#§
CKMB (IU/L) (Mean± SD)	13.5 (10-19)	14.5 (10-18)	33 (27-53) #§
LDH (U/L) (Median, IQR)	190 (165-208)	96.2* (72.4-110)	89.9# (76-120)
Troponin	0.13 (0.09-0.15)	0.15 (0.09-0.21)	0.28 (0.1-0.8) #

QR: inter-quartile range, eGFR: estimated glomerular filtration rate, CK: creatine kinase, LDH: lactate dehydrogenase, *: indicates significance between Groups I and IIA, #: indicates significance between Groups I and IIB, \$: indicates significance between Groups IIA and IIB. NS: non-significant.

Table 3: Statistical significance of microRNA-155-5p in the studied groups

miR	Group I (n=60)	Group IIA (n=30)	Group IIB (n=30)
microRNA-155-5p (median, IQR)	1.07 (0.81-1.34)	4.88* (2.51-7.35)	27.66#\$ (17.98-39.21)

IQR: inter-quartile range, *: significance between Groups I and IIA, #: significance between Groups I and IIB, \$: significance between Groups IIA and IIB. NS: non-significant.

Table 4: Results of the receiver operating characteristic (ROC) curve to discriminate the power of miR-155-5p to differentiate between the studied groups

Parameters	A	B	C	D
Area Under the Curve	0.941	0.882	1.00	0.946
P-value	<0.001	<0.001	<0.001	<0.001
95% Confidence Interval	Lower bound	0.889	0.783	1.00
	Upper bound	0.993	0.981	1.00
Cut-off value	>1.834	1.834	5.214	>14.55
Sensitivity %	91.7	83.3	100	90
Specificity %	93.3	93.3	100	93.3
PPV%	96.49	92.59	100	93.32
NPV%	84.85	84.85	100	90.32
Accuracy %	92.22	88.33	100	91.67

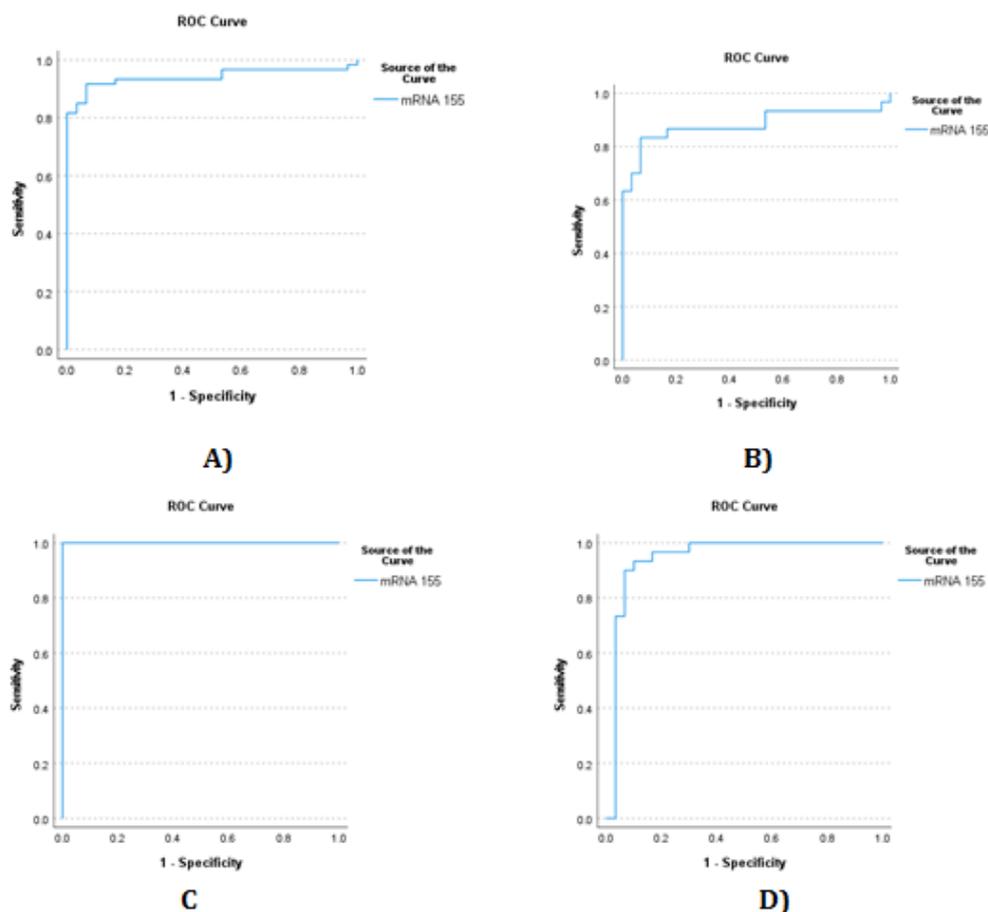


Figure 1: ROC curve detecting patient groups from control using miR-155-5p. ROC curve for discrimination between A) cases and control groups, B) control and Group IIA, C) control and Group IIB, and D) Group IIA and Group IIB

These results align with those of Beltrami *et al.* (2018), who concluded a statistically significant increase in the urinary miR-155 in DKD patients compared with the healthy controls and diabetic patients without DKD. They concluded that urinary miR-155 is a promising biomarker to detect DKD with 80.61% sensitivity and 52% specificity [31].

Conclusion

MiR-155-5p detection by RT-PCR proved valuable for the CKD diagnosis. The results of this study highlights the significance of serum miR-155-5p as a noninvasive marker for discriminating CKD with and without cardiovascular complications.

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Authors' contributions

All authors contributed equally in this manuscript regarding selecting the criteria of patients, analyzing the data, writing, and revising the paper.

Conflict of Interest

The author declared that they have no conflict of interest.

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