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Original Article

The Effect of miR-34a and miR-34b Polymorphisms on Clinical-Pathological Characteristics of Renal Cell Carcinoma

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HIGHLIGHTS

- Changes in miRNA binding sites or their sequences may affect the interaction of mRNA-miRNA target sites, thus, leading to a change in the regulation of target gene expression.
- MiRNAs are more powerful biomarkers in the detection of cancers than other molecular biomarkers.
- Numerous studies have shown the association between cancer risk and miR-SNPs.

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ABSTRACT

Introduction
MicroRNAs can regulate expression of gene by binding to 3'-UTRs (untranslated region) of mRNAs. Genetic changes in miRNA binding domains affect susceptibility to various diseases, including cancer. This research presented to determine the impact of pri-miR-34b T> C rs4938723 and miR34a A>C rs6577555 polymorphism in renal cell carcinoma.

Methods
This case-control study has been done on 100 patients with RCC and 100 healthy matched control in two referral urology canters in Tehran, Iran. The miRNA-34a/b polymorphisms mentioned in the genomes of healthy individuals and patients with RCC were studied by the tetra arms PCR method. Then statistical studies were performed by SPSS software, using the independent sample T-test and Chi-square. A P-value lower than 0.05 is significant.

Results
The connection between pri-miR-34b T>C and miR34a A>C variants were considered according to age, sex, tumor site, metastasis site, tumor stage, and tumor grade in this study. No statistically significant difference existed between the two study groups regarding gender and age. Smoking and alcohol consumption were significantly higher in RCC patients, so we suggest them as the main risk factors. The rs6577555 polymorphism showed a significant association with the classification of tumor type (P-value=0.047), but rs4938723 SNP did not correlate with the tumor type.

Conclusions
The findings indicated that rs4938723 and rs6577555 polymorphism might be a risk for predisposition to RCC in population of Iran. More research with greater sample sizes and various ethnicities must approve our findings.

Keywords: miRNAs; Risk Factor; Cancer; Renal Cell Carcinoma

Introduction

Renal cell carcinoma (RCC) is a predominant kind of kidney cancer in which malignant cells form in the kidney's tubules. RCCs account for approximately %2 to 3% of all adult malignancies scenarios. It can be classified into three major subgroups, such as a clear cell (ccRCC), chromophobe (chRCC), and papillary (pRCC) (1). People may not be aware of having cancer at all until the cancer is in its later stages. Most cases are diagnosed incidentally on imaging, ultrasound, CT scan, and MRI (2). Kidney cancer survival rates depend heavily on the tumor stage and the treatment selection. Most cases of RCC are detected between 50 and 70 years of age (3, 4).

The usual symptoms of RCC are haematuria, flank pain, unintentional weight loss, loss of appetite, abdominal mass, and abnormal liver function (5). Kidney cancer survival rates depend heavily on the tumor stage and the treatment selection. Nonetheless, the overall patient survival rate is still low (6). The well-established predisposing factors for renal cell carcinoma are hypertension, obesity, family history, cigarette smoking, and aromatic hydrocarbon (6, 7). MiRNAs (MicroRNAs) are the large class of short non-coding RNAs (ncRNA) that span between 18-25nt. Post-transcriptionally, they regulate the multiple genes expression by binding to the mRNA of the coding genes (8, 9). Early evidence of the role of miRNAs in human cancer was revealed in the pathogenesis of chronic lymphocytic leukaemia (CLL). One of the most common cytogenetic abnormalities observed in more than 80% of B-CLL patients is 13q14.3 deletions.

According to the report, microRNAs have many roles in the biological mechanisms related to tumorigenesis, including apoptosis, stress response, cell-cycle regulation, and Immune response. So, they are promising candidates for biomarker development (10-12). Evidence recommends that miRNAs are abnormally expressed in renal cell carcinoma and have notable parts in malignancies' onset, progression, and metastasis. Any change in miRNA binding sites or their sequences may affect the interaction of mRNA-miRNA target site, thus, leading to a change in the regulation of target gene expression (13).

Several studies have concentrated on the connection between miR-34 family members and tumorigenesis of several malignancies, such as hepatocellular carcinoma (HCC). Xu et al., acknowledged that SNP rs4938723 in the promoter region of pri-miR-34a/b,c may contribute to hepatocellular carcinoma susceptibility (14).

In this paper, we investigated whether pri-miR-34b T>C rs4938723 and miR34a A>C rs6577555 polymorphism increase the risk of RCC and affect the outcome of patients with renal cell carcinoma in the Iranian population.

Methods

Study subjects and DNA Extraction

This research was performed based on the declaration of Helsinki (IR.SBMU.UNRC.1397.33). An informed written consent was signed by patients. Generally, 100 renal cell carcinoma patients and 100 controls were enrolled in this Case–Control study. Samples were collected from RCC patients who were treated in Modares and Labbafinejad hospital from September 2016 to September 2020. A total of Peripheral blood samples were gathered in EDTA containers and stored at -80 C° for further molecular analysis. Genomic DNA was extracted from 5ml peripheral blood samples by the salting-out method. The two miRNA SNPs chosen for this paper were pri-miR-34b T>C rs4938723 and miR34a A>C rs6577555. We used Amplification refractory mutation system polymerase reaction chain (T-ARMS-PCR) assays to analyze these SNPs. We also tested the relationship between these polymorphisms and clinicopathologic data, including tumor stage, grade, tumor type, age, gender, lymph-node involvement, distant metastasis, etc. The role of SNP was measured with the comparison of allele frequency of miRNAs in the patient group to that in control groups.

T-ARMS-PCR primers design and genotyping

For genotyping of 200 human samples, T-ARMS-PCR assays were applied. Two missense SNPs, and four pairs

Table 1. Primer sequences and product size for the T-ARMS-PCR assay of miR-34a and pri-miR-34b gene polymorphisms

SNP		Primer	Sequence 5´ - 3´	PCR product
rs4938723	T>C	Forward inner primer (C allele)	CCTCTGGGAACCTTCTTTGACCTCTC	202
		Reverse inner primer (T allele)	AGAAGGGAGGTCCTCAATGAGAGCTTTA	142
		Forward outer primer	TCACAAGATACTGTTTTTCTGGCATCCA	290
		Reverse outer primer	TAGTCAAATAGTGAGCCAGGCAGCTTGT	290
rs6577555	A>C	Forward inner primer (A allele)	ACCAGCCTGGTTAACATAGCCAGATCA	194
		Reverse inner primer (C allele)	CATTTTGTAGAGACAGTTGCTGAAGGTAGG	266
		Forward outer primer	CGTGCCTGTAGTCCTAGCTACTGGAGAG	403
		Reverse outer primer	TCAACCACTGTCCTTTTCGAATTTTTTC 640	403

of primers were found and designed following the rules (Table 1). The PCR reactions were performed in a total volume of 25μL, containing 10pmol of each of the inner primers, 10pmol of each of the outer primers, 10mM of Amplicon PCR master mix 1×, and 100ng of DNA. An initial denaturation at 95 °C for 5min is used to perform the PCR amplification profile preceded by denaturation at 95°C for 1min (32 cycles), annealing at 54 °C (32 cycles), and extension at 72 °C for 45min (32 cycles), preceded by a last extension for 5min. The products were detected by electrophoresis in 1.5% agarose gel stained with ethidium bromide at an onstant voltage (100 V) for 40min.

Statistical analysis

A paired T-test was applied to investigate the differences in levels of miRNAs between patient and control groups. By using the student's T-test or Chi-square test, differences between the two groups were analyzed. We used Pearson's correlation coefficient analysis. A P-value<0.05 was considered statistically significant. Many variables were adjusted, including age, gender, drinking status, smoking, and clinicopathological characteristics.

Results

Study subject characteristics

In this study, the 100 RCC cases, including 67(50.4%) males and 33(49.3%) females with an overall mean age of 55±12 years, and 100 cases without renal cancer, including 66(49.6%) males and 34 (50.7%)females with an overall mean age of15±51 years, were compared. No statistically significant difference was found between the two study groups regarding age and gender (P-value=0.54 and 0.5, respectively).

Table 2 shows the comparison of subjects with and without RCC based on weight loss, anorexia, positive personal history, positive family history, myalgia smoking, alcohol consumption, and drug use. We identified that smoking, alcohol consumption, and drug use rates were lower in the control group than in the RCC patients' group ,and 27% of all patients had lost weight symptoms, while this number was 9 in the control group.

Presence of comorbidities and clinical characteristics

In this study, we compared the number of comorbidities in the patient and control groups with an overall percentage. The prevalence of specific comorbidities in the RCC patients' group was: diabetes (n=16, 43%), hypertension (n=32, 42.6%), hyperlipidemia (n=12, 34.2%), cardiovascular diseases (n=16, 34.7%) and the prevalence of comorbidities in the control groups was: diabetes (n=21, 57%), hypertension (n=43, 57.3%), hyperlipidemia (n=23, 65.8%), cardiovascular diseases (n=30, 65.3%). It is essential to note that several patients had more than one comorbidity.

Descriptive statistics

We identified differences between groups based on site distribution, clinical/pathological stage, presence of clinical/pathological nodal metastasis, differentiation grade, and lymphatic invasion by histology. The most usual kind of RCC was clear cell type (61%). 61% of the cases were clear cell type, and 13% were mucinous carcinoma. The majority of patients were in the T3 stage (81%), while 27 and 68% showed lymphatic vessel invasion and nodal metastasis, respectively. Data analysis showed that most patients were of clear cell type (61%).40% cases were at T1a stage while 21% of them were at T3a and t1b stage. 59% of cases were right-sided. The RCC was located at the lower pole in four out of thirteen patients (30%), at the upper pole in 29% of cases, at the lower-middle and upper-lower-middle in 3% of patients, and in the upper-middle in four cases (4%). The primary tumor location was the middle pole in thirty-one cases (31%). When we analyzed our data, according to Fuhrman nuclear grading system, we found that 19% belongs to grade I, 44% to grade II, 21% to grade III, and 16% belong to grade IV (Table 3).

Table 2. Association between RCC and baseline information of patients

Variables	Patients (N:100)	Controls (N:100)	Total	P-value
	Number	Number	Number	
Weight loss	27	9	36	0.001
Decreased appetite	20	10	30	0.048
Myalgia	21	10	31	0.032
Positive Personal history	2	0	2	0.156
Positive Family history	1	0	1	0.317
Smoking	21	7	28	0.004
Opium	10	1	11	0.005
Alcohol consumption	6	0	6	0.013

Table 3. Clinical characteristics of RCC cancer cases and controls

Feature	Number	Percentage
Stage		
T1aNxMx	34	34
T1bNxMx	16	16
T2NxMx	11	11
T3aNxMx	17	17
T3bN1Mx	7	7
T3bN2Mx	5	5
T3bNxMx	6	6
T4NxMx	4	4
Total	100	100
Tumor type		
Papillary type1	10	10
Papillary type2	6	6
Choromophob	12	12
Clear cell	60	60
Rcc oncocytic	2	2
Scc	1	1
Adenocarcinoma	0	0
Rcc unclacified	0	0
Sarcomatoeid	2	2
Conventional	3	3
Celecting duct carcinoma	2	2
Metastatic	1	1
Metanephric stroma	1	1
Total	100	100
Tumor location		
Upper pole	29	29
Lower pole	30	30
Middle pole	31	31
Upper-middle	4	4
Lower-middle	3	3
Upper-lower-middle	3	3
Laterality		
Right	59	59
Left	41	41
Tumor grade		
I	21	21
II	42	42
III	21	21
IV	16	16

Table 4. The distributions of genotypes for the miRNA polymorphisms pri-miR-34b T>C rs4938723 and miR34a A>C rs6577555 in RCC patients and control cases

SNP	Case/Control	TT	CT	CC
rs4938723 T>C	Patients (N: 100)	33 (33%)	45 (45%)	6 (6%)
	Controls (N: 100)	42 (42%)	44 (44%)	14 (14%)
	Total (N: 200)	75	89	19
	P-value	0.189	0.887	0.060
SNP	**Case/Control**	**AA**	**CA**	**CC**
rs6577555 A>C	Patients (N: 100)	36 (36%)	41 (41%)	23 (23%)
	Controls (N: 100)	43 (43%)	44 (44%)	13 (13%)
	Total	79	85	36
	P value	0.312	0.668	0.066

Association of the rs4938723 SNP and rs6577555 SNP with renal cell carcinoma risk

The distributions of genotypes for the miRNA polymorphisms pri-miR-34b T>C rs4938723 and miR34a A>C rs6577555 in RCC patients and control cases are illustrated in Table 4. We observed that pri-miR-34b CC and miR34a CC genotypes were more frequent in both groupes, but no statistically significant difference was in the distribution of the other genotypes between RCC cases and the control group.

Subgroup analysis according to RCC subtype

We examined the association of the two miRNA SNPs with each RCC subtype. We observed that rs6577555 polymorphism revealed a significant association with tumor type (P-value=0.047), but rs4938723 SNP were not related to the classification of tumor subtype (P-value=0.42) (Table 5).

We compared persons with and without RCC based on lymph node involvement, distant metastasis, surgical margin status, perineural invasion, Perivascular invasion, Perirenal Fat Invasion, and adrenal invasion. Rs4938723 polymorphism revealed a remarkable association with perirenal Fat Invasion (P-value=0.020), distant metastasis (P-value=0.03), and lymph node involvement (P-value=0.02) as patients.

Rs4938723 polymorphism revealed a significant association with tumor stage (P-value=0.025), but rs6577555 SNP did not relate to the classification of malignant tumors stage (P-value=0.38) (Table 6).

The results showed a significant connection between the rs4938723 polymorphism and tumor grade of RCC patients (P-value=0.018), but no significant correlation was detected between the pri-miR-34b rs4938723 variant and tumor types (P-value=0.42). Rs6577555 polymorphism revealed a significant correlation with tumor types of RCC subjects (P-value=0.047), but rs6577555 SNP did not associate with their tumor grade of them (P-value=0.11) (Table 7).

Table 5. Association of the pri-miR-34b T<C rs4938723 and miR34a A<C rs6577555 genotypes

Tumor type	Rs6577555			Rs4938723		
	AA	AC	CC	TT	CT	CC
Papilary type1	5	3	2	5	5	0
Papilary type2	2	3	1	0	6	0
Choromophob	2	8	2	2	9	1
Clear cell	17	33	10	27	30	3
RCC oncocytic	0	2	0	0	2	0
Squamous Cell Carcinoma	1	0	0	0	0	1
Adenocarci-noma	0	1	0	0	0	0
RCC unclacified	0	0	0	0	0	0
Sarcomatoid	0	1	1	0	1	1
Conventional	2	1	0	1	2	0
Collecting duct carcinoma	1	1	0	1	1	0
RCC metastatic	1	0	0	0	1	0
Metanephric stromal	1	0	0	1	0	0
Total	32	52	16	37	57	6

Table 6. Comparison between gene genotypes and pathological stage

SNP	Pathologic stage	TT	CT	CC	Total
Rs4938723 (P-value=0.025)	T1a	16	16	8	40
	T1bNxMx	5	15	1	21
	T2NxMx	5	1	1	7
	T3aNxMx	3	11	7	21
	T3bNxMx	2	1	2	5
	T3bN1Mx	0	1	2	3
	T3bN2Mx	2	0	0	2
	T4NxMx	0	0	1	1
	Total	33	45	22	100
	Pathologic stage	AA	AC	CC	Total
Rs6577555 (P-value=0.38)	T1a	13	19	8	40
	T1bNxMx	10	7	4	21
	T2NxMx	2	3	2	7
	T3aNxMx	8	9	4	21
	T3bNxMx	2	1	2	5
	T3bN1Mx	0	1	2	3
	T3bN2Mx	1	1	0	2
	T4NxMx	0	0	1	1
	Total	36	41	23	100

Discussion

In This paper, we discovered that rs4938723 in pri-miR-34b and rs6577555 in miR34a were linked to the development of RCC in Iranian population. Both variants did not correlate with age and sex in RCC patients, but pri-miR-34b rs4938723 polymorphism is more frequent in RCC grade 2/4. According to the results, CC genotype for both rs4938723 and rs6577555 is correlated with distant metastasis and lymph node involvement.

MicroRNAs are small groups of ncRNAs that are now recognized as the primary regulator of gene activity. Numerous studies have shown the association between cancer risk and miR-SNPs. when SNPs in miRNA genes could possibly affect miRNA biogenesis and change target selection, much attention has been paid to evaluating the assosiation between the cancer risk and variation in microRNAs (15). MiR-34a and miR-34b are a member of the highly conserved miR-34 family. The mir 34 family, like the let7 family, is one of the leading families of TSmirs families. This family includes three memberes: miR-34a, miR-34b, and miR-34c (16).

A study by Zhang S and colleagues showed that miR-34 rs4938723 is a potentially functional variation in the promoter area associated with RCC risk in a Chinese population (17). A meta-analysis study indicated the association between microRNA-34b/c rs4938723 polymorphism and risk for cancer development (18). Another meta-analysis highlighted that hsa-miR-34b/c rs4938723 polymorphism might have a contradictory role in various malignancies (19). A study by Wang X. et al., showed a ramarkable connection between the rs4938723 polymorphism and cancer risk in the codominant model of various cancer types, such as osteosarcoma, nasopharyngeal cancer, and kidney cancer (20).

A study by Yan Sun et al., was conducted to investigate the association of SNPs in the hsa-miR-34a regulatory region with diabetes mellitus (DM) or diabetic nephropathy (DN) susceptibility. Three SNPs (rs12128240, rs2666433, rs6577555) in miR-34a were analyzed in Type 2 diabetes mellitus (T2DM) patients with or without DN and normal controls (21). A study by Zhang S and colleagues revealed no significant association between rs12128240 or rs6577555 and ischemic stroke (IS) found in the Chinese population (22).

Several studies indicate the role of hsa-miR-34a polymorphism in different malignancies, both in tumor formation and poor prognosis of patients (23, 24). Several studies indicate the role of hsa-miR-34a polymorphism in different malignancies, both in tumor formation and poor prognosis of patients (24). Both Mutations in the P53 gene and deletion of the short arm of chromosome 1 are connected to lower levels of miR-34a. MiR-34a plays as a TSmir and physically affects the proto-oncogene MET and targets its function In head and neck squamous cell carcinoma (HNSCC) (23).

Conclusions

This study aimed to determine signature of miRNA that could recognize RCC blood serum of patients and

Table 7. Comparison between gene genotypes and tumor grade with RCC tumor type

Polymorphism	Tumor Grade	CC	CT	TT	Total
Rs4938723	1/4	3	10	6	19
	2/4	11	18	15	44
	3/4	5	8	8	21
	4/4	3	9	4	16
	Total	22	45	33	100
	Tumor Grade	**AA**	**AC**	**CC**	**Total**
Rs6577555	1/4	6	6	7	19
	2/4	9	19	16	44
	3/4	4	11	6	21
	4/4	4	5	7	16
	Total	23	41	36	100

healthy controls, and confirm distinguished miRNAs as potential biomarkers for RCC. The results of these studies identified that pri-miR-34b T>C rs4938723 and miR34a A>C rs6577555 polymorphisms helped predict the severity of kidney cancer as well as patients' survival rate and might be used in the future as diagnostic biomarkers or targets for treatment that require observations. In order to approve our findings, greater sample sizes and various ethnicities are required in future studies.

Authors' contributions
All authors contributed equally.

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Conflict of interest
All authors declare that there is no potential competing or conflict of interest.

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Ethics statement
This research was performed in accordance with the declaration of Helsinki (IR. SBMU.UNRC.1397.33). Participants provided informed written consent to participate in the study.

Data availability
Data will be provided on request.

Abbreviations
Arms PCR Amplification refractory mutation system polymerase reaction chain
CLL Chronic lymphocytic leukaemia
DM Diabetes mellitus
DN Diabetic nephropathy
HCC Hepatocellular carcinoma
HNSCC Head and neck squamous cell carcinoma
IS Ischemic stroke
MiRNA Micro RNA
RCC Renal Cell Carcinoma
SNP Single nucleotide polymorphism
T2DM Type 2 diabetes mellitus

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Author (s) biosketches

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