

# HEMATOLOGICAL PARAMETERS IN HEPATOCELLULAR CARCINOMA AND microRNA-223 GENE ASSOCIATED WITH HEPATITIS VIRUS IN LOCAL AREA



M.S. Al-Janaby<sup>a</sup>, R.H. Abdujaleel<sup>a</sup>, M.A. Najm<sup>b</sup>, R.T. Mohsen<sup>a</sup>, A.K. Alalwani<sup>a</sup>

<sup>a</sup> College of Science, University of Anbar, Al-Anbar, Iraq

<sup>b</sup> College of Medicine, Ibn Sina University of Medical and Pharmaceutical Sciences, Baghdad, Iraq

**Abstract.** *Background.* Hepatocyte function may be altered by chronic HBV and HCV infections through similar mechanisms that influence the onset of hepatocellular cancer. This current work points to examine the function of microRNA-223 in Iraqi hepatocellular carcinoma (HCC) patients induced by hepatitis virus. MicroRNA-223 served as calibrator to explore its evaluate disease progression and diagnosis. *Materials and methods.* Blood samples were then drawn from 20 people (males and females and different ages), some of them were latterly diagnosed with HCC. these blood samples were used later for molecular study to find target gene expression. *Results.* The importance of HCV, HBV, and liver cancer was examined in this study, along with the drop in research and studies conducted in Iraq. Those who got treatment had somewhat higher levels of microRNA-223 countenance, whereas those who were diagnosed early and did not get treatment had lower levels. MicroRNA-223 appearance stages were meaningfully lower in the first phase of hepatitis samples than in standard samples ( $p < 0.0001$ ), which may indicate that microRNA-223 can be used as a biomarker to monitor conduct effectiveness. It is recommended that more research done in this area to help in diagnosis. *Conclusion.* MicroRNAs are an essential tool for early diagnosis and for monitoring the onset and progression of disease due to their great specificity and reliability. all results hat HCC patients with HBV and HCV expressed miR-223 at lower levels than healthy controls. Some hematological and parameters differed significantly from those in the control group.

**Key words:** microRNA-223, hepatocellular carcinoma, expression, hepatitis B, hepatitis C, biomarkers, Iraqi patients.

## ГЕМАТОЛОГИЧЕСКИЕ ПОКАЗАТЕЛИ ПРИ ГЕПАТОЦЕЛЛЮЛЯРНОЙ КАРЦИНОМЕ И ГЕН МИКРОРНК-223, АССОЦИИРОВАННЫЙ С ЛОКАЛЬНЫМ ВИРУСОМ ГЕПАТИТА

Аль-Джанаби М.С.<sup>1</sup>, Абуджалил Р.Х.<sup>1</sup>, Нажм М.А.<sup>2</sup>, Мохсен Р.Т.<sup>1</sup>, Алавани А.К.<sup>1</sup>

<sup>1</sup> Университет Анбар, г. Аль-Анбар, Ирак

<sup>2</sup> Университет медицинских и фармацевтических наук имени Ибн Сины, Багдад, Ирак

**Резюме.** *Введение.* Функция гепатоцитов может изменяться при хронических инфекциях, вызванных вирусами гепатита В и С, посредством сходных механизмов, ведущих к развитию гепатоцеллюлярного рака. Целью настоящей работы было изучение функции микроРНК-223 у иракских пациентов с гепатоцеллюлярной карциномой (ГЦК), вызванной вирусом гепатита С. МикроРНК-223 служила калибратором для оцен-

### Адрес для переписки:

Рана Талиб Мохсен  
Тел.: +964-78-13549676; +964-77-33523407.  
E-mail: rana2011@uoanbar.edu.iq

### Contacts:

Rana Talib Mohsen  
Phone: +964-78-13549676; +964-77-33523407.  
E-mail: rana2011@uoanbar.edu.iq

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ки прогрессирования заболевания и диагностики. *Материалы и методы.* Образцы крови были получены от 20 человек (мужчин и женщин разного возраста), у некоторых из них впоследствии была диагностирована ГЦК. Образцы крови были в дальнейшем использованы для молекулярного анализа экспрессии целевых генов. *Результаты.* В данном исследовании изучались ассоциации между обнаружением вирусов гепатита С и В и раком печени, а также сокращение количества исследований в этой области, проводимых в Ираке. У тех, кто получал лечение, уровень микроРНК-223 был несколько выше, тогда как у лиц, кому диагноз был поставлен на ранней стадии, и кто не получал лечения, уровень был ниже. Уровень экспрессии микроРНК-223 в образцах первой фазы гепатита был значительно ниже, чем в контрольных образцах ( $p < 0,0001$ ), что может указывать на возможность использования микроРНК-223 в качестве биомаркера для мониторинга эффективности лечения. Рекомендуется проведение дополнительных исследований в этой области для повышения эффективности диагностики. *Заключение.* Разные микроРНК являются важным инструментом ранней диагностики и мониторинга начала и прогрессирования заболевания благодаря своей высокой специфичности и надежности. Полученные результаты свидетельствуют о том, что у пациентов с ГЦК при гепатите В и гепатите С экспрессия miR-223 была ниже, чем у здоровых лиц контрольной группы. Ряд гематологических показателей и параметров достоверно отличались у пациентов от таковых в контрольной группе.

**Ключевые слова:** микроРНК-223, гепатоцеллюлярная карцинома, экспрессия, гепатит В, гепатит С, биомаркеры, иракские пациенты.

## Introduction

Chronic contagions instigated by hepatitis B and C viruses can alter hepatocyte function and perhaps use similar mechanisms to promote the growth of hepatocellular carcinoma (HCC). Systemic treatment is necessary for most patients with advanced stage HCC, and sorafenib is now the drug most frequently prescribed [1, 2, 4]. The main culprits are hepatitis viruses, however alcohol, certain medications, and other autoimmune diseases cause infections. Patients with hepatitis C are 15–40% more likely to develop liver cancer and cirrhosis [3]. MicroRNA has variable actions related to different biological processes such as apoptosis, immunity, and cancer metastasis [5, 6]. It has been found that MicroRNA-223 gene expression is effected during HCC [7, 8]. When it comes to identifying HCC in its early stages, the miR-122 has limited diagnostic value. Moreover, miR-122 is a host that is necessary for the transmission of HCV. Antivirals can be used in addition to already available treatments like interferon's and direct-acting antivirals since they can target miR-122. The expression of microRNA-223, an essential part of innate defense [9, 10, 11]. MiR-223 expression is often upregulated in Recurrent ovarian and colorectal malignancies and downregulated in leukemia and HCC. Occasionally, a high tumor burden, an aggressive disease, and an unfavorable outlook for the patient have been associated with downregulated miR-223. Understanding the intricate function that miR-223 plays in cancer detection and treatment is therefore crucial. The character of miRNAs in dissimilar cancer types has been the subject of several investigations [12, 13]. miR-223 has demonstrated broad evolutionary conservation in the X chromosome's q12 region. Despite this, little is understood about the specific roles that miR-223 plays in human HSCs and how it may be used therapeutically to cure fibrosis. Using primary human HSCs, miR-223 suppresses fibrogenic activity and prolifer-

ation while promoting quiescent HSC traits such lipid reaccumulation and retinol storage. Moreover, HSC cell contraction and motility were decreased by miR-223 activation [14]. Additionally, miR-223 overexpression inhibited many hepatocyte targets, preventing liver fibrosis brought on by NASH. In order to avoid liver fibrosis, neutrophil based EV scan transmit miR-223 to HSCs, and miR-223 downregulation activates HSCs [15]. According to estimates, HCC, the greatest public histological subtype, accounted for between 75 and 90 percent of all new liver cancers (LCs) identified globally in 2018. LC increased by 12.4% between 2008 (696 000) and 2012 (782 000), and by 7.6% between 2012 and 2018 (841 080). Some studied found that hepatitis B (HBV) DNA fragment can enter the host's genome and induce ROS generation, which can harm host DNA and lead to gene alterations and finally HCC even when the hepatitis C (HCV) genome cannot be incorporated into the host genome [16, 17]. This study examines the association of microRNA-223 with HCC in hepatitis Iraqi patients. It also evaluates its potential significance in disease development and diagnosis.

## Materials and methods

*Study area.* The patient groups included in this study were three, HCC patients group, HBV patients group and finally HCV patients group. These patients groups were studied between February–July 2023.

*Sample collection.* The blood samples were collected from 78 individuals with different ages and sex and were divided as follow; 30 from healthy individuals, 14 samples from HBV patients, 14 samples from HCV patients and 20 samples from HCC patients. Then, laboratory tests were performed. Regarding HCC patients, many of them had not yet started treatment. On the other hands, some of them were with advanced cancer so they started external radiation therapy in conjunction with chemotherapy

**Table 1. Primers used in current work**

miR-223RT	5' GTCGTATCCAGTGCCTGTCTGGAGTCGGCAATTGCACTGGATACGACGGGGTA 3'
miR-223F	5' TGTCAGTTTGCAAA 3'
miR-223R	5' CAGTGCCTGTCTGGAGT 3'

drugs. The samples were collected from the Teaching Oncology Hospital at Medical City and Yarmouk Teaching Hospital. These individuals had no prior medical history of liver cancer or HBV or HCV infection. They also did not exhibit any symptoms of liver cancer or type B or C hepatitis.

*Specific primers of microRNAs.* About 75–150 bp were adopted for PCR amplicon as given in Table 1.

*Quantification of microRNAs.* This miRNA quantification kit made it simple to identify microRNAs, siRNAs, and single- and double-stranded RNAs. Among the contaminants, it may tolerate detergents, salts, and solvents. Compared to large mRNA or rRNA, it is designed to select only small RNA.

*Measurement of Gene Expression.* By utilizing the adopted method for gene expression measurement was the relative cycle threshold ( $2^{-\Delta\Delta Ct}$ ), to give fold fluctuations as an expression measurement of the mature RNAs'. This ratio was counted by correlating the expression levels of the test to the healthy groups. While values greater than one reflect increment in gene expression, and numbers between zero and one reflect reduction in the gene expression, a one-fold change implies no change. The target genes' expressions were normalized by establishing the proper thresholds to obtain accurate Ct values from the RT-qPCR apparatus.

*Biostatistical analysis.* Statistical analysis was used to identify the differences in the levels of biomarkers gene expression among the three patient groups on hand, and between patients and control group on the other hand.

*Ethical Consideration.* By Al-Anbar University Research, Issue 233, dated June 3, 2023. To preserve the confidentiality and identities of patients, no images of patients, healthy subjects, or any part thereof were used in the research.

## Results and discussion

*Expression of microRNA-223 in HCC.* As shown in Table 2, the relationship between microRNA (miRNA) dysregulation and the onset of cancer has been extensively studied in recent years. The miRNAs that are differently expressed in HCC are still mostly unknown. Regardless of viral ties, two markedly dysregulated miRNAs, miR-223, can help differentiate HCC from neighboring nontumoral livers. The study revealed that STMN1 protein levels in HCC cell lines were decreased as a result of miR-223 restoration. Furthermore, reporter constructs containing the 3' untranslated region of STMN1 showed that miR-223 readily suppressed luciferase activity ( $p \leq 0.0002$ ) [18]. Furthermore, HCC tissues

and cell lines with a greater risk of metastasis had decreased levels of miR-223 [19].

*Expression of MiR-223 in HBV.* As shown in Table 3, HBV and HCC are considered among the liver diseases in which dysregulation of miR-223 expression has been demonstrated. Furthermore, miR-223 levels are correlated with the degree of hepatic damage and patient prognosis, suggesting that it may be a prognostic biomarker for liver diseases [20, 21].

*Expression of MiR-223 in HCV.* Table 4 show that the qualified crease change indicates that miR-223 expression was downregulated. We also used the following formula to compute the crease modification for each sample: Patients' fold change is equal to  $2^{-\Delta\Delta Ct}$ . The analytical technique (unpaired t-test) revealed an important alteration between the two samples (HCV and healthy control), with a p value  $< 0.0001$ . The results are consistent with other studies presenting that miR-223 levels are reduced in various viral hepatic diseases, such as cirrhosis, HCC, hepatic damages induced by alcohol or chemicals, viral hepatitis, and other hepatic diseases [22, 23]. Also, there is an indication that miR-223 modulated a variety of immune cascades and it had been found that viral hepatitis and other infectious diseases are associated with abnormal expression of miR-223, therefore, its essential uses as a therapeutic and diagnostic target, has been the subject of several recent studies [24, 25, 26].

The findings and a summary of the miR-223 concentrations in samples from patient groups and control samples were also demonstrated by using a map. The previously reported style (Relative Fold Change) which depend on the miR-223 expression was used to correlate patient groups to control samples.

**Table 2. Housekeeping gene and microRNA223 gene in control and HCC patient samples**

Sample	HKG Ct	GOI Ct	$\Delta Ct$	$\Delta\Delta Ct$	P
Control	27.666	32.122	5.578	0	0.0001****
HCC	28.111	34.543	7.783	1.999	

**Table 3. Housekeeping gene and microRNA223 gene in control and HBV patient samples**

Sample	HKG Ct	GOI Ct	$\Delta Ct$	$\Delta\Delta Ct$	P
Control	27.754	33.454	4.174	0	0.0001****
HBV	28.111	37.433	7.439	2.545	

**Table 4. Housekeeping gene and microRNA223 gene in control and HCV patient samples**

Sample	HKG Ct	GOI Ct	$\Delta Ct$	$\Delta\Delta Ct$	P
Control	29.342	33.876	3.883	0	0.0001****
HCV	29.654	35.876	6.222	2.565	

**Table 5. Hepatocellular carcinoma blood tests**

Test	Healthy	Patients	Over all samples	P Value
WBC	17 (20)	3 (20)	20	0.42
LYM%	15 (20)	5 (20)	20	0.355
GRAN%	16 (20)	4 (20)	20	0.366
LYM#	17 (20)	3 (20)	20	0.377
GRAN#	0 (20)	20 (20)	20	0.001***
RBC	9 (20)	11 (20)	20	0.0481 *
HGB	8 (20)	12 (20)	20	0.0344*
HCT	7 (20)	13 (20)	20	0.0322*
MCV	12 (20)	8 (20)	20	0.0844
MCH	14 (20)	6 (20)	20	0.59
PLT	7 (20)	13 (20)	20	0.0432*
MPV	10 (20)	10 (20)	20	0.039*
PDW	2 (20)	18 (20)	20	0.001***
PCT	0 (20)	20 (20)	20	0.001***

Additionally, the heat map explained the reduction in target gene expression in different patient samples. Furthermore, using normal one-way ANOVA techniques, there was a significant difference miR-223 concentration between the HBV and HCV groups ( $p < 0.0001$ ). This advises that reduction in miR-223 expression might be consistent biomarkers for differentiating between healthy samples and HBV and HCV infections.

*Hematology study in HCC Patients.* According to the obtained data, Granulocyte count (GRAN) was found to be substantially aberrant when correlated to the healthy people group ( $p \leq 0.001$ ). Furthermore, other hematological parameters were also significantly altered in comparison to the healthy people group ( $p \leq 0.005$ ), which include hematocrit (HCT), red blood cell (RBC), platelet count (PLT), and mean platelet volume (MPV), hemoglobin (HGB), as shown in Table 5.

The proportion of HCC patients with normal and abnormal hematological distributions in relation to normal values is shown in Table 5. In people with HCC, there was a statistically significant connection ( $p \geq 0.05$ ) between normal and abnormal PCT, normal and abnormal PDW, and normal and abnormal GRAN. Normal and abnormal RBC count, normal and abnormal HGB, normal and abnormal HCT, normal and abnormal PLT, and normal and

abnormal MPV were also shown to be statistically significantly correlated ( $p \geq 0.05$ ). Other indicators, however, did not exhibit a statistically significant association. The results are consistent with the investigation’s conclusions. The study discovered that while the mean values of white blood cell counts and concentrations significantly decreased, the mean values of hemoglobin, hemoglobin and plasma proteins (PLATS), and red blood cell counts and concentrations significantly decreased when compared to similar values in the control group [27].

The study found that as people age, their chance of developing HCC rises.

Table 6 shows that the range of ages at diagnosis was 20–70 years old, with an average age of 43 years. It was shown that the greatest proportion of HCC cases occurred in people aged 61 to 70. The results of current work agreed with the result of another study which declared that people older than forty are more likely to have HCC compare to other ages [28].

Age and gender had a significant impact on HCV incidence rates, with younger males and women having the greatest rates. Between the ages of 21 and 30, HCV infections gradually increased for both genders. In 2020, there was a significant incidence of acute hepatitis C infections among those aged 20–39 years, which was also the age range who took overdoses and injection drug in the US [28]. The mean age of HBV patients in the 30- to 40-year-old age group was 30 to 40. According to Ryerson A.B. et al. (2020), this conclusion is consistent with earlier studies [23].

In order to monitor the biomarkers and gather bigger samples of patients who are not receiving therapy, more extensive research on miR-223 expression in HCC is required.

These biomarkers have also been suggested as follow-up tests for patients both through and after therapy due to their high levels of sensitivity and specificity. It can also be regarded as a sign of the advancement of HCC in people with hepatitis B or C virus infections.

Furthered clinical studies are necessary to examine the possibility that microRNA might be a promising therapeutic in the future [29].

## Conclusion

MicroRNAs are valuable tools for the detection and diagnosis of the disease in the early stages and also for accurately preventing disease worsening or recurrence. Their presence in individuals previously infected with the HBV or HCV may serve as an indicator of HCC development. Further extensive research on miR-223 expression in HCC is necessary to monitor biomarkers and collect larger patient samples, especially those not undergoing therapy. Utilizing microRNAs as biomarkers for disease progression, early detection, and post-treatment recurrence is highly recommended due to their high sensitivity

**Table 6. Age range distribution of different studied group**

Group	HCC	HCV	HBV	Healthy people
10–20	1	2	–	1
21–30	1	8	5	4
31–40	–	2	5	10
41–50	4	8	10	9
51–60	7	4	4	2
61–70	9	–	–	3
71–80	–	–	–	1

and specificity. These biomarkers can also serve as follow-up tests during and after therapy and may indicate HCC advancement in hepatitis B or C patients. Additionally, further clinical studies are essential to approve the significant importance of microRNAs as a novel target for a future therapeutic approach.

## Significance statement

This current work conducted the importance of miR-223, as a novel marker for the early detection, prognosis, and monitoring of HCC. These biomarkers

can be beneficial for detecting disease progression, assessing recurrence, and guiding personalized treatment strategies, especially in patients with HBV or HCV. The study highlights the significance of microRNAs in enhancing diagnostic accuracy and therapeutic monitoring. This data conducted in this study can be utilized in other larger studies to lift the veil on the importance of the microRNA in the disease detection and therapeutic applications. Thus, an advanced notion on the action of microRNAs in HCC progression and treatment may be arrived at, paving the way for novel clinical and therapeutic advancements.

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**Авторы:**

**Аль-Джанаби М.С.**, PhD, доцент кафедры биотехнологии, факультет естественных наук, Университет Анбара, г. Аль-Анбар, Ирак;

**Абдуджалил Р.Х.**, PhD, преподаватель кафедры биотехнологии, факультет естественных наук, Университет Анбара, г. Аль-Анбар, Ирак;

**Наджм М.А.**, PhD, доцент кафедры фармакологии, медицинский факультет, Университет медицинских и фармацевтических наук Ибн Сины, Багдад, Ирак;

**Мохсен Р.Т.**, PhD, доцент кафедры биотехнологии, факультет естественных наук, Университет Анбара, г. Аль-Анбар, Ирак;

**Алалвани А.К.**, ассистент преподавателя кафедры биотехнологии, факультет естественных наук, Университет Анбара, г. Аль-Анбар, Ирак.

**Authors:**

**Al-Janaby M.S.**, PhD, Assistant Professor, Department of Biotechnology, College of Science, University of Anbar, Al-Anbar, Iraq;

**Abdujaleel R.H.**, PhD, Lecturer, Department of Biotechnology, College of Science, University of Anbar, Al-Anbar, Iraq;

**Najm M.A.**, PhD, Assistant Professor, Department of Pharmacology, College of Medicine, Ibn Sina University of Medical and Pharmaceutical Sciences, Baghdad, Iraq;

**Mohsen R.T.**, PhD, Assistant Professor, Department of Biotechnology, College of Science, University of Anbar, Al-Anbar, Iraq;

**Alalwani A.K.**, Assistant Lecturer, Department of Biotechnology, College of Science, University of Anbar, Al-Anbar, Iraq.

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