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The diagnostic value of lncRNA UCA1 in multiple myeloma patients in relation to miRNA-331-3p

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ABSTRACT

Background: One type of malignant plasma cell disease is multiple myeloma (MM). MiR-331-3p contains the potential binding sites of LncRNA human urothelial carcinoma associated 1 (UCA1). The purpose of this study was to assess the significance of serum lncRNA UCA1 to MM diagnosis in relation to miRNA-331-3p. **Methods:** This study type was a case-control observational design. Serum from 53 patients with MM who were recently diagnosed and 53 age- and sex-matched healthy controls was collected. The expressions of lncRNA UCA1 and miRNA 331-3p were detected by real-time qPCR. **Results:** The lncRNA UCA-1 was highly expressed in MM patients, and miRNA 331-3p was down-expressed. Serum lncRNA UCA-1 levels were significantly increased with ISS stages. However, lncRNA UCA-1 expression levels did not differ with Durie-Salmon stages, renal dysfunction, and bone damage. On the other hand, miRNA 331-3p expression levels were significantly reduced with Durie-Salmon stages and bone damage. The lncRNA UCA-1 expression showed a sensitivity and specificity of 88.7% and 100%. The miRNA 331-3p expression showed a sensitivity and specificity of 83% and 100%. Multivariate analysis showed that lncRNA UCA1 (p=0.016) and miRNA 331-3p (p=0.008) were independent predictors for MM diagnosis. **Conclusions:** High expression of lncRNA UCA1 was detected in myeloma patients, which increased significantly with ISS. The miRNA331-3p was downregulated in MM. Both markers seem to be predictors for MM diagnosis, but the lncRNA UCA1 showed higher sensitivity and specificity. The lncRNA UCA1 and miRNA 331-3p were independent predictors for MM diagnosis.

Introduction

Tumor cells in multiple myeloma (MM), a malignant plasma cell disease, develop from bone marrow plasma cells. Clonal growth of plasma cells in the bone marrow is the origin of myeloma-related conditions including hypercalcemia, renal failure, anemia, or bone disorders [1]. MM accounts for about 10% of all hematological cancers [2].

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The incidence rate of MM is higher in males and rises with age, especially beyond 40 years of age. In Egypt, there were an estimated 552 MM patients in 2015; however, the number continued to rise thereafter [3]. The majority of patients have significant skeletal and renal involvement along with a variety of systemic illnesses upon presentation; among inpatients, MM has the third-highest mortality after liver and lung cancer [4, 5].

Despite advances in treatment, MM is an incurable disorder; over 20% of patients die or relapse within two years of being diagnosed [6, 7]. Treating MM requires the development of novel therapeutic, prognostic, and diagnostic targets.

The current, invasive, and time-consuming approach of diagnosing MM involves a thorough immunotyping procedure following bone marrow puncture, serological markers, and imaging. Prompt diagnosis of MM and prompt medical intervention can significantly enhance the prognosis of MM patients and dramatically lower patient mortality. Although albumin and β_2-microglobulin can already be utilized as MM supplemental diagnostic criteria, adequate biological markers are still lacking [8]. Therefore, discovering new markers is crucial.

A significant subgroup of highly conserved non-coding RNAs (ncRNAs) with at least 200 nucleotides and little capacity to code for proteins are known as long non-coding RNAs (lncRNAs). LncRNAs may be tumor biomarkers because of the cumulative evidence that they are dysregulated in many cancer types and may affect the pathophysiological processes of cancer at different levels, such as transcription and translation [9]. Research indicates that lncRNAs can either accelerate or slow the development of human cancers by sponging the target microRNA (miRNA) as a competitive endogenous RNA (ceRNA) [10].

LncRNA human urothelial carcinoma associated 1 (UCA1), which is comprised of 1442 nucleotides, was initially discovered in bladder cancer and identified as a biomarker in multiple cancer types [11]. MiR-331-3p contains the potential binding sites of UCA1 [12]. It was revealed that UCA1 promotes proliferation and inhibits apoptosis by enhancing interleukin-6 receptor (IL6R) expression and further activating the JAK2/STAT3 signaling pathway by sponging miR-331-3p [10]. So, the purpose of this study was to assess the significance of serum lncRNA UCA1 in the diagnosis of MM in relation to miRNA-331-3p and to study their correlations with the prognostic features of the disease. As far as we are aware, this is the first study to emphasize the significance of these markers in MM patients from Egypt.

Subjects and Methods:

Study design:

This study type was a case-control observational design. In Zagazig University Hospitals (Zagazig, Egypt) from January 2024 to April 2025, this study was conducted. As an ethical issue, the study was carried out in compliance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). The Institutional Review Board (Faculty of Medicine, Zagazig University #10176) gave its approval to this research. This study consent form was read, understood, and signed by all subjects. This study was reported according to the strengthening of the reporting of observational studies in epidemiology (STROBE) guidelines.

Subjects:

A 95% confidence interval (CI) and 80% statistical power were used to determine the sample size.

The mean and standard deviation of lncRNA UCA1 in cases and controls were obtained from a previous study [10]. The sample size estimate showed that 106 participants were needed, with 53 in each group. Our study comprised 53 newly diagnosed MM subjects and 53 healthy controls who were matched for age and sex. Every MM patient met the requirements for MM diagnosis. Patients were excluded if they had any other coexisting malignancy, inflammatory or autoimmune diseases.

Sampling:

Plain vacutainer tubes (Becton Dickinson & Co., USA) were used to collect blood samples. Samples were obtained for 30 minutes, and tubes were centrifuged for 10 minutes at 1200 xg. The serum was aliquoted immediately in 2 microcentrifuge tubes. One was utilized for chemistry tests, and the other aliquot was stored at − 80 °C until RNA extraction. An EDTA tube was collected to assess the hemoglobin.

Method:

Laboratory tests:

A complete blood count was performed using the XS500i Hematology analyzer **(Sysmex,**

Kobe, Japan). The Cobas 8000-C702 Modular Analyzer was used to measure calcium, creatinine, and albumin. The Cobas 6000-C501 Modular Analyzer was used to measure the light chains, immunoglobulins, and β2 microglobulins. The Cobas analyzers were supplied by Roche, Germany.

LncRNA UCA 1 and miRNA331-3p expression:

The assessment of LncRNA UCA 1 and miRNA331-3p expression was performed by real-time qPCR. The miRNeasy Serum/Plasma Kit (QIAGEN, GmbH, Hilden, Germany) was used to extract total RNA. Using a Thermo Scientific (USA) NanoDrop-2000 spectrophotometer, the amount and quality of the extracted RNA were assessed.

Following the manufacturer's instructions, 1 μg of extracted RNA was used to create the cDNA using the miScript RT II kit (QIAGEN GmbH, Hilden, Germany). Until it was analysed, the cDNA was kept at -80°C. Using the miScript SYBR Green PCR kit (QIAGEN, GmbH, Hilden, Germany), the qRT-PCR was carried out in accordance with standard protocol. The Stratagene Mx3005P qPCR System (Agilent Technologies, Germany) was used to identify the expression of lncRNA UCA1and miRNA 331-3p (Supplementary Figure 1). U6 and GAPDH were employed as internal controls. A fold change in the relative expression of miRNA 331-3p and lncRNA UCA1 was reported using the $2^{-\Delta\Delta CT}$ method. The primers were designed by Metabion (Germany) by the following sequences (Table 1).

Statistical analysis

The study parameters showed a non-normally distributed pattern, according to the Shapiro-Wilk test. Parameters were compared using the Kruskal-Wallis H test, Dunn's test, Chi-squared and Mann-Whitney U tests. Receiver operating characteristic (ROC) analysis was employed to evaluate the marker's diagnostic efficacy. Spearman's correlation and logistic regression analysis were applied. A significance level of $p < 0.05$ was applied throughout the study, which was conducted using the statistical program SPSS 20.0 (Chicago, IL, USA).

Results:

Table 2 provides a summary of the clinicopathological characteristics of MM patients and controls. There was no discernible difference between the two groups' demographic statistics. ISS-III and Durie-Salmon stage III accounted for the largest percentage of MM patients (39.6% and 73.6%, respectively). Group differences in laboratory parameters were statistically significant ($p<0.05$).

This study assessed the levels of miRNA 331-3p and lncRNA UCA-1 expression in serum samples from 53 healthy controls and 53 MM patients. The findings demonstrated that MM patients' serum had elevated levels of lncRNA UCA-1 expression. MM patients, however, had decreased expression of miRNA 331-3p (Figure 1, $p<0.001$).

Serum lncRNA UCA-1 expression levels were significantly increased with ISS stages. However, lncRNA UCA-1 expression levels were not differ with Durie-Salmon stages, renal dysfunction, and bone damage. On the other hand, miRNA 331-3p expression levels were significantly reduced with Durie-Salmon stages and bone damage (Figure 2).

ROC curves were created using our relevant information in order to examine the properties of miRNA 331-3p and lncRNA UCA-1 expression as possible tumor markers for MM. MM patients and healthy people were successfully differentiated by LncRNA UCA-1 expression, with an AUC of 0.952 (95% CI= 0.908-0.955; $p < 0.001$). Figure 3 shows that the AUC for miRNA 331-3p was 0.944 (95% CI = 0.896-0.992; $p < 0.001$). The sensitivity, specificity, PPV, and NPV of lncRNA UCA-1 expression were 88.7%, 100%, and 89.8% at a threshold of 1.35. The expression of lncRNA UCA-1 has a diagnosis accuracy of 94.3%. The sensitivity, specificity, PPV, and NPV of miRNA 331-3p expression were 83%, 100%, 100%, and 85.5%, respectively, at a cutoff of 1.35. The expression of miRNA 331-3p had a 91.5%

Table 3 demonstrates a positive correlation between creatinine and β2 microglobulin and the expression of lncRNA UCA1 in the MM group. There was a statistically significant negative connection between miRNA 331-3p and lncRNA UCA1. In contrast, there was a negative correlation between miRNA 331-3p and IgG and IgA.

A multivariate statistical analysis was conducted to verify that the expressions of miRNA 331-3p and lncRNA UCA1 are useful biomarkers for the diagnosis of MM (Table 4). The diagnosis of MM was found to be substantially correlated with albumin, anemia, calcium, β2-microglobulin, lncRNA UCA1, and miRNA 331-3p in univariate analysis. A multivariate analysis of these variables

showed that only miRNA 331-3p (p=0.008) and lncRNA UCA1 (p=0.016) were independent predictors for the diagnosis of MM.

Table 1: Primers sequences that were utilized in this study

Target	Forward	Reverse
lncRNA UCA1	**5'-CTCTCCATTGGGTTCACCATTC-3'**	**5'-CTCTCCATTGGGTTCACCATTC-3**
miR-331-3p	**5'-GCGCCCCTGGGCCTATC-3'**	**5'-CGATGACCTATGAATTGACA-3'**
U6	**5'-ACCCTGAGAAATACCCTCACAT-3'**	**5'-GACGACTGAGCCCCTGATG-3');**
GAPDH	**5′-TCCTCTGACTTCAACAGCGACAC-3′**	**5′-CACCCTGTTGCTGTAGCCAAATTC-3′**

Table 2: Demographic, clinical, and laboratory data

Parameters	MM patients (No.: 53)	Controls (No.: 53)	p
Age	**51 [33-67]**	**49 [30-63]**	**0.12**
Sex (Male/Female)	**35/18 (66/34)**	**32/21 (60.4/39.6)**	**0.55**
ISS stage:			
I	**15 (28.3)**		
II	**17 (32.1)**		
III	**21 (39.6)**		
Durie-Salmon stage:			
I	**8 (15.1)**		
II	**6 (11.3)**		
III	**39 (73.6)**		
Heavy chain type			
IgG, g/L	**7.7 [2-15.2]**		
IgA, g/L	**2.1 [1.2-8.5]**		
Light chain type			
Kappa, mg/L	**4.9 [1.4-14.1]**		
Lambda, mg/L	**12.4 [9.2-52.1]**		
Anemia	**35 (66)**		
Hypercalcemia	**14 (26.4)**		
Renal dysfunction	**11 (20.8)**		
Bone Lesions	**38 (71.7)**		
Laboratory findings			
Hemoglobin, g/dL	**9.2 [7.5-12.4]**	**10.7 [8.1-14.2]**	**0.001***
Albumin, g/dL	**3.9 [2.8-5.3]**	**4 [3.9-4.4]**	**0.025***
Creatinine, mg/dL	**0.99 [0.7-2.6]**	**0.78 [0.6-1]**	**<0.001***
β2 microglobulin, mg/L	**4.5 1.5-18.2]**	**1.7 [0.9-3.9]**	**<0.001***
Calcium, mg/dL	**10.2 [8.4-15.2]**	**9.4 [8.8-10.2]**	**0.002***

MM: Multiple myeloma; ISS: International Staging System; Ig: Immunoglobulin

Data are expressed as median [min-max] or number (%)

****: Significant***

Table 3: Correlation study of factors associated with diagnosis of MM

Parameters	LncRNA UCA1		miRNA 331-3p	
	rs	p	rs	P
Age	0.24	0.08	0.14	0.32
Hemoglobin	-0.16	0.22	0.04	0.75
Albumin	0.13	0.37	-0.08	0.56
Creatinine	0.29	0.036*	0.07	0.61
β2 microglobulin	0.62	0.008*	-0.11	0.39
Calcium	0.11	0.42	0.05	0.97
IgG	0.19	0.17	-0.31	0.023*
IgA	0.07	0.61	-0.36	0.008*
Kappa	0.07	0.62	0.12	0.39
Lambda	0.08	0.58	0.23	0.1
miRNA 331-3p	-0.28	0.04*	1	------

Table 4: Univariate and multivariate analysis of factors associated with diagnosis of MM

Variables	Univariate		Multivariate	
	OR (95% CI)	p	AOR (95% CI)	p
Age	1.04 (0.99-1.08)	0.08	1.17 (0.88-1.55)	0.28
Sex	1.28 (0.58-2.8)	0.55	5.2 (0.08-341)	0.44
Albumin	0.36 (0.14-0.94)	0.038*	0.08 (0.001-5.3)	0.24
Anemia	4.5 (1.9-10.2)	<0.001*	0.35 (0.012-9.8)	0.53
Calcium	2.4 (1.4-3.84)	0.001*	0.98 (0.22-4.2)	0.97
β2-microglobulin	45.6 (9.9-208.7)	<0.001*	1.3 (0.01-160.9)	0.92
LncRNA UCA1	130.5(30.8-552)	<0.001*	277 (2.7-2765)	0.016*
miRNA 331-3p	0.002(0-0.21)	<0.001*	0.001 (0-0.12)	0.008*

OR: Odds ratio; AOR: Adjusted odds ratio; CI: Confidence interval.

Figure 1: Expression of lncRNA UCA1 and miRNA-331-3p in MM patients.

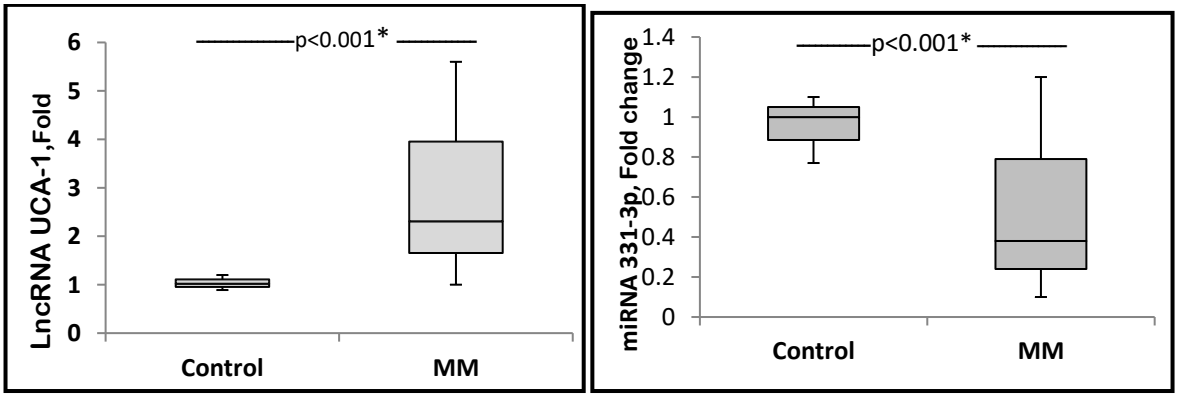
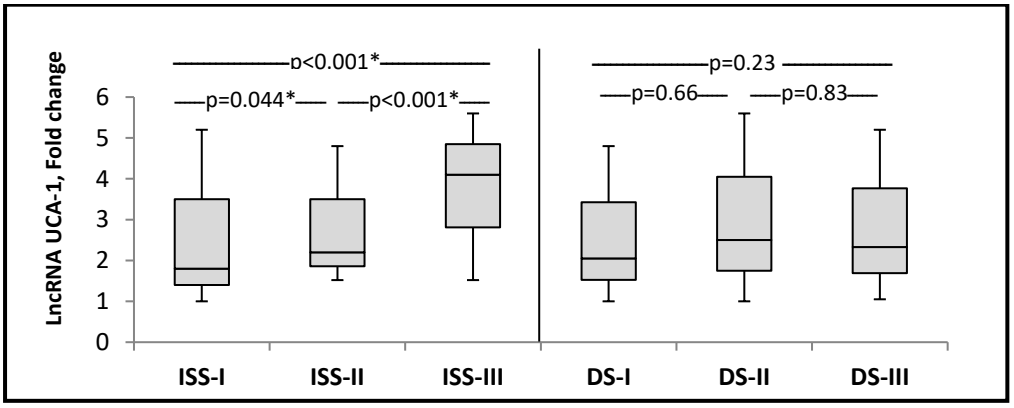
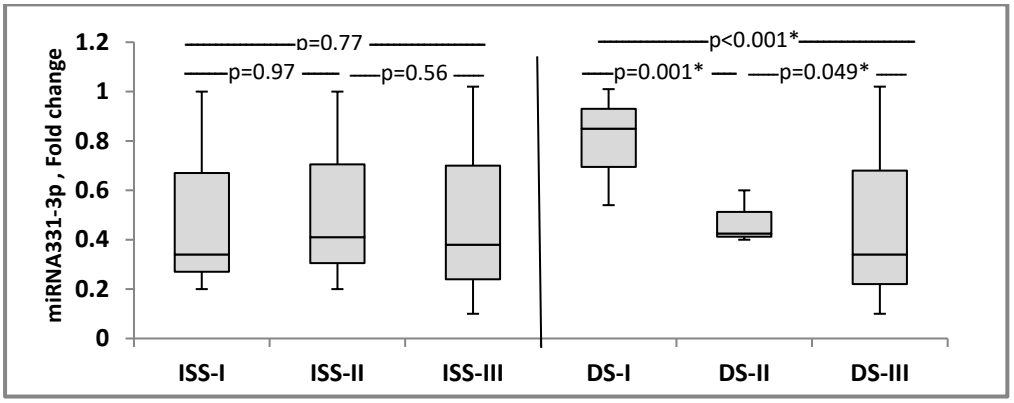
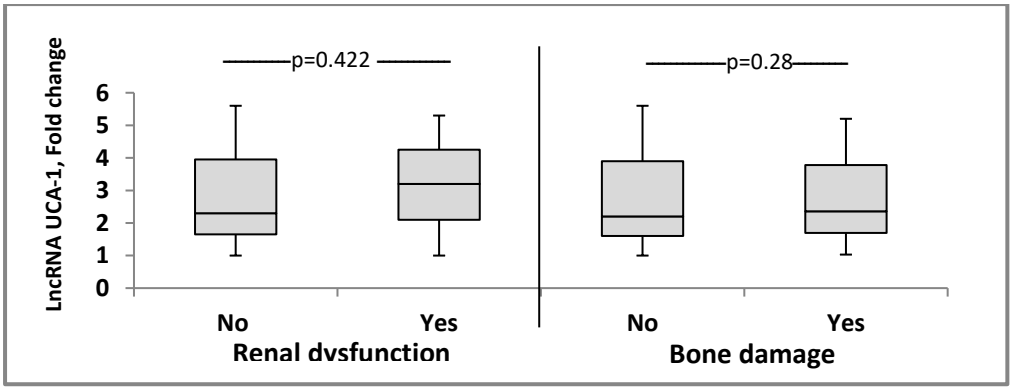
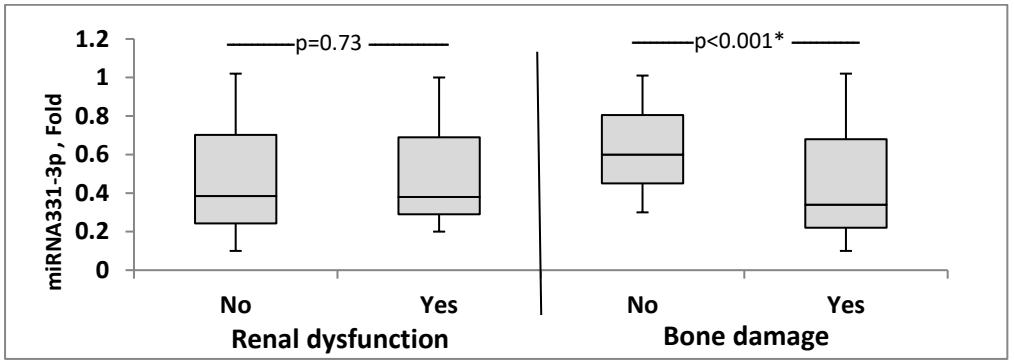


Figure 2: Analysis of the relationship between lncRNA UCA1 and miRNA-331-3p with clinical parameters.



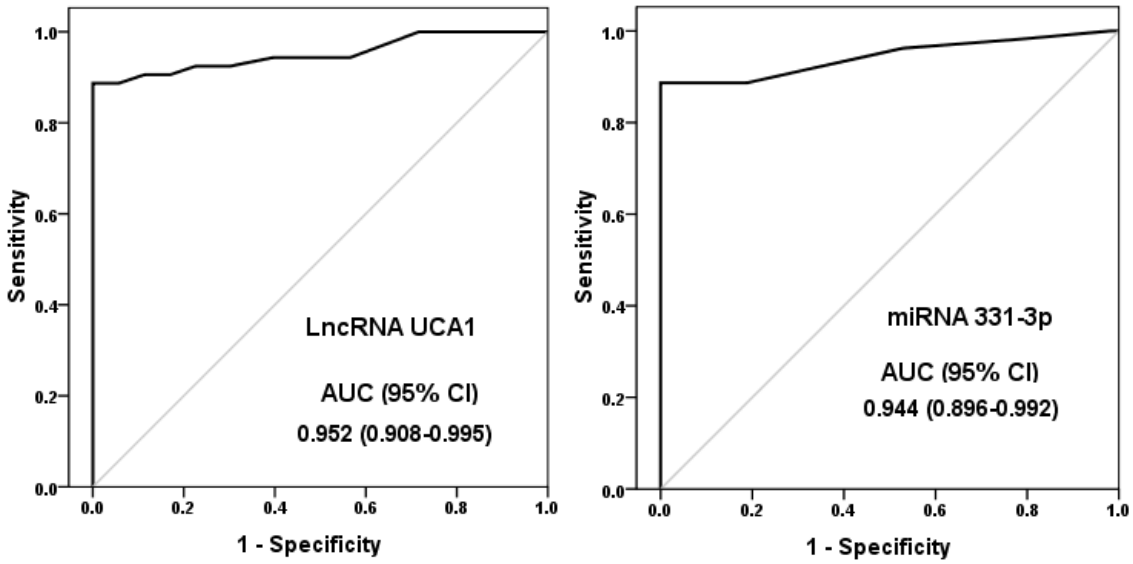






ISS: International Staging System; DS: Durie-Salmon stage. *: Significant

Figure 3: ROC curves analysis for MM prediction



AUC: Area under curve; CI: Confidence interval

Discussion

Since many lncRNAs have been found to be aberrantly expressed in tumors. LncRNAs are reference molecules and potential biomarkers for illness risk assessment, and they have a close relationship with pathological signs and the prognosis of MM [13]. LncRNAs can communicate with mRNAs by competing for shared miRNAs [14].

By functioning as a ceRNA of several miRNAs, UCA1 can control several pathways. Consequently, it can regulate a number of biological processes. Therefore, UCA1 may be employed as a biomarker for disease diagnosis [15]. Thus, this study aimed to evaluate the role of serum lncRNA UCA1 in the diagnosis of MM in relation to miRNA-331-3p and to study their correlations with the prognostic features of the disease.

This study revealed that lncRNA UCA-1 was increased in the serum of MM patients. However, miRNA 331-3p was down-expressed. These results agreed with the findings of Li et al. [10], UCA1 increases IL6R expression via sponging miR-331-3p, which promotes proliferation and prevents apoptosis of MM in vivo experiments.

According to the results of the current investigation, the sensitivity and specificity of lncRNA UCA-1 expression were 88.7% and 100%, respectively. Following ROC curve analysis validation, UCA1 expression levels demonstrated 85% sensitivity and 94.7% specificity, according to Sedlarikova et al. [16].

Regarding this study, in myeloma patients, lncRNA UCA-1 was positively correlated with serum β2 microglobulin and creatinine. Significantly, both miRNA 331-3p together with lncRNA UCA-1 were negatively correlated, while IgA with IgG showed negative correlation with miRNA331-3p. According to Sedlarikova et al. [16], there's a negative correlation between serum albumin and lncRNA UCA-1 expression level. But lncRNA UCA-1 expression level was positively correlated with M-Ig serum levels. In our research, no correlation was found between LncRNA UCA1 and different types of M protein; on the contrary, Sedlarikova et al. [16] found a positive correlation indicating a potential link between UCA1 and unique myeloma performance.

Serum lncRNA UCA-1 expression levels were significantly increased with ISS stages. This agreement with Sedlarikova et al. [16] found a correlation between advanced ISS stage and greater UCA1 levels. As β2-microglobulin is a cornerstone in ISS reflecting kidney function, it was postulated that high UCA1 expression is associated with renal failure in myeloma patients [17]. This disagrees with our results, although UCA1 expression is increased with ISS stages but does not differ in Durie-Salmon stages or with renal failure.

The current study found that miRNA-331-3p was downregulated in myeloma patients [18]. This supports the earlier discovery that miR-331-3p

may act as a tumor suppressor, preventing tumors from developing malignant characteristics [19]. Additionally, miR-331-3p was downregulated in MM, and in MM cells, miR-331-3p targeted the insulin-like growth factor 1 (IGF-1) receptor [20].

IgA and IgG in this study exhibit a negative connection with miRNA-331-3p. Conversely, bone damage and Durie-Salmon stages were associated with significantly lower levels of miRNA 331-3p expression. Malignancy invasion, metastasis, and cell proliferation were all markedly reduced by overexpression of miR-331-3p [21]. Additionally, osteosarcoma development and incidence were impacted by miR-331-3p [22].

For the diagnosis of MM, the expression of miRNA 331-3p demonstrated a sensitivity and specificity of 83% and 100%, respectively. As indicators to detection of cancer, miRNAs have been investigated extensively [23].

This study has limitations even if it offered some insights. The study involved a limited or homogeneous sample size, the findings may not be generalizable to broader or more diverse MM populations. Variables such as treatment status, or other genetic factors might influence serum levels and were not controlled for, potentially impacting the results. The study may require longer follow-up periods to validate the prognostic significance of these biomarkers reliably. Future research should therefore be carried out with a larger sample size, across several locations, and with more thorough clinical pathological features.

Conclusion:

High expression of lncRNA UCA1 was detected in myeloma patients, which increased significantly with ISS. The miRNA331-3p was downregulated in MM. Both markers seem to be predictors for MM diagnosis, but the lncRNA UCA1 showed higher sensitivity and specificity. The lncRNA UCA1 and miRNA 331-3p were independent predictors for MM diagnosis.

Conflict of Interest:

Authors declare no conflict of interest

Financial Disclosures:

This research did not have any funds.

Supplementary files:

Supplementary Figure 1

Authorship:

Abeer A. Fikry: Conceptualization, Investigation, Writing – Review & Editing.

Marwa Esawy: Conceptualization, Methodology, Formal analysis, Writing – Review & Editing.

Amir Abd-elhameed: Methodology, Visualization, Writing- Original Draft.

Ahmed B. Waley: Methodology, Investigation, Writing- Original Draft.

Rania M. Abdullah: Methodology, Investigation, Writing- Original Draft, Supervision.

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