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Research Article

The Expression of Serum lncRNA MIR17HG in Patients with Multiple Myeloma and Its Clinical Significance

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Objective. Multiple myeloma (MM) represents a malignant tumor with abnormal proliferation of plasma cells. The current study sought to investigate the changes in serum lncRNA MIR17HG (long noncoding RNA miR-17-92a-1 cluster host gene) levels in MM patients and its values in assessing the accuracy of MM diagnosis and predicting diagnosis. *Methods*. First, 108MM patients and 85 healthy controls were enrolled as the study subjects. The serum levels of MIR17HG in all subjects were determined by RT-qPCR. MM patients were clinically staged according to the Durie-Salmon (DS) and international staging system (ISS), and the levels of serum MIR17HG were compared among patients at different stages. The correlation of serum MIR17H level with serum creatinine (Scr), lactate dehydrogenase (LDH), and albumin (ALB) was analyzed using the Pearson method. The accuracy of the serum MIR17HG level in identifying MM was evaluated using receiver operating characteristic curves. The progression-free survival (PFS) and overall survival (OS) curves of MM patients were plotted using the Kaplan–Meier method. *Results*. Serum MIR17HG levels were up-regulated in MM patients and elevated with the development of DS and ISS stages. The serum MIR17HG was positively correlated with Scr and LDH and negatively correlated with ALB in MM patients. Serum MIR17HG level >1.485 could evaluate the accuracy of identifying MM. The PFS and OS were significantly shortened in MM patients with elevated MIR17HG levels. *Conclusion*. Our findings collectively indicate that the serum MIR17HG can aid the evaluation of accurate MM identification, and a high serum MIR17HG level can predict poor prognosis of patients with MM.

1. Introduction

Multiple myeloma (MM) represents an incurable plasma B-cell malignancy, characterized by monoclonal malignant plasma cell proliferation and monoclonal immunoglobulin production. Unfortunately, the 5-year survival rate of MM is approximately 10–30% lower than that of other hematologic tumors [1]. The initial clinical presentation of MM includes musculoskeletal pain, anemia, and susceptibility to infection, while the later stage is characterized by fractures, pancytopenia, renal insufficiency, and the development of certain neurological signs [2]. Despite significant advances in the field of MM diagnosis and treatment modalities in the form of chemotherapy, autologous/allogeneic stem cell transplantation, and monoclonal antibody therapy using drugs such as daratumumab, elotuzumab, indatuximab, and SAR650984, the clinical outcomes of MM remain unsatisfactory [3, 4]. The pathogenesis of MM is highly intricate, and the detailed underlying mechanism of its occurrence and development requires much more elaboration [2]. In lieu of the same, it is of urgent significance to elucidate the potential pathogenesis of MM and to explore for potential treatment strategies.

Long noncoding RNAs (lncRNAs) are a type of noncoding RNA with a length of more than 200 nucleotides and are renowned for their critical roles in gene expression, transcriptional regulation, translation, and protein modification [5]. A plethora of evidence has unearthed that lncRNAs are aberrantly expressed in a wide array of human cancers including MM and are associated with tumorigenesis and the prognosis of cancers [6]. Interestingly, lncRNAs are also regarded as diagnostic and prognostic

biomarkers for solid tumors [7, 8]. One such lncRNA, namely, MIR17HG, is located on chromosome 13q31 and plays an indispensable role in augmenting tumorigenesis, cancer cell proliferation, and tumor metastasis [9]. MIR17HG is universally overexpressed in osteosarcoma, cervical squamous cell carcinoma, glioma, colorectal cancer (CRC), and other tumors and further exerts carcinogenic effects in the process of carcinogenesis [10]. Intriguingly, lncRNA MIR17HG acts in a microRNA- and DROSA-independent manner and provides an important chromatin scaffold for myeloma growth [11]. Moreover, MIR17HG exhibits a carcinogenic role during osteosarcoma tumorigenesis *via* the miR-130a-3p/SP1 axis [12]. In addition, MIR17HG can promote liver metastasis of CRC by mediating a glycolysis-associated positive feedback circuit [13]. However, a very limited number of studies have explored the relationship between serum MIR17HG and MM at present. Accordingly, the current study set out to investigate the clinical value of serum MIR17HG levels in the accurate identification of MM and prognostic prediction of MM patients.

2. Materials and Methods

2.1. Study Subjects. First, a total of 108 symptomatic MM patients newly diagnosed at the Bozhou People's Hospital from June, 2016, to June, 2018, were consecutively enrolled in the study. The inclusion criteria were as follows: (1) patients were newly diagnosed with MM in accordance with International Myeloma Working Group (IMWG) criteria of MM [14]; (2) aged >18 years; and (3) without other hematological malignancies or solid tumors. Exclusion criteria were as follows: (1) patients presented with smoldering (asymptomatic) myeloma; (2) plasmablastic lymphoma; (3) a history of chemotherapy or radiotherapy; (4) a history of stem cell transplantation; and (5) pregnant or lactating women. Additionally, 85 healthy individuals were recruited from June, 2016, to June, 2018, to serve as healthy controls (HCs). Following venous blood collection, all patients were administered induction therapy with lenalidomide/bortezomib/dexamethasone in accordance with the IMWG guidelines [15].

2.2. Data Collection. Collection of baseline clinical data included the following: (a) demographic characteristics (age and gender); (b) immunoglobulin content; (c) bone conditions (e.g., bone lesions); (d) renal function status (e.g., renal impairment); (e) biochemical indicators (e.g., hemoglobin (Hb), calcium, serum creatinine (Scr), albumin (ALB), β2-microglobulin (β2-MG), and lactate dehydrogenase (LDH)); and (f) clinical stage (Durie-Salmon (DS) stage and international staging system (ISS) stage) [16, 17].

2.3. Reverse Transcription Quantitative Polymerase Chain Reaction (RT-qPCR). Fasting venous blood samples (approximately, 5 mL) were collected the next day following enrollment and the samples were centrifuged (1000 g, 10 minutes). Subsequently, the serum samples were pipetted into tubes and stored at −80°C until further analysis. The total RNA content was extracted from 300 μL of the serum using serum RNA extraction kits (Life Technologies, Foster City, CA, US), followed by determination of RNA purity and concentration by means of ultraviolet spectrophotometry. Thereafter, the collected RNA samples were stored at −80°C for subsequent analyses.

The extracted RNA was reverse-transcribed into cDNA using reverse transcription kits (Thermo Fisher, Waltham, MA, USA) in compliance with the manufacturer's instructions. Briefly, cDNA was synthesized from total RNA using gene-specific primers. The reverse transcriptase reaction contained 5 ng of RNA sample, and 10 μL of RT master mix consisting of 2 μL of 100 mM dNTP mix, 1 μL reverse AidRNAse reverse enzyme, 4 μL of 5 × reactive buffer, 1 μL of 20 U/μL ribolock RNase inhibitor, 1 μL of nuclease-free water and 1 μL of stem-loop Olig (DT) primer. Afterwards, 20 μL of the reaction mixture was incubated at 42°C for 60 minutes, followed by 72°C for 5 minutes, and finally preserved at 4°C.

Real-time PCR was carried out on ABI 7500 PCR detection system (ABI, CA, USA). The 20 μL PCR reaction mixture consisted of 10 μL SYBR green I (S9430, Merck KgaA, Darmstadt, Germany), 3 μL cDNA, 1 μL forward primer, 1 μL reverse primer, and 5 μL RNase-free H_2O. Next, the samples were placed in optical plates at 95°C for 10 minutes, followed by 40 cycles of 95°C for 15 seconds, and 60°C for 31 seconds. The relative expression levels of MIR17HG were estimated using the $2^{-\Delta\Delta Ct}$ method, with glyceraldehyde-3-phosphate dehydrogenase (GAPDH) serving as the internal reference. Primer sequences are illustrated in Table 1.

2.4. Follow-Up. All patients were followed up for a total of 48 months until June 30, 2022. Progression-free survival (PFS) was defined as the period from the initial treatment to disease progression or death, and overall survival (OS) was defined as the time span from the initial treatment to death. The patients not known to have disease progression or died at the last follow-up were censored on the date of last visit or on the date of last known to be alive.

2.5. Statistical Analysis. SPSS21.0 statistical software (IBM, Armonk, NY, USA) and GraphPad Prism 8.0 software (GraphPad, San Diego, CA, USA) were utilized for statistical analysis and plotting. The normality of continuous variables was checked using the Kolmogorov–Smirnov test and normally distributed variables were expressed as *mean* ± *standard deviation* (SD). Nonnormally distributed variables were expressed as medians (interquartile range) and categorical variables were expressed as counts (percentages). The *t*-test or Mann–Whitney *U* test was adopted to evaluate comparisons between groups, and one-way analysis of variance (ANOVA) was performed to assess comparison among multiple groups, and Tukey's test was carried out for the post-hoc test. Correlation between lncRNA MIR17HG in sera of MM patients and biochemical parameters was

Table 1: Primer sequences of RT-qPCR.

Primers	Forward (5′-3′)	Reverse (5′-3′)
MIR17HG	GGCGTCCCGTCGTAGTAAAG	CATTGTGTCAGGAGTCAGTGTGTC
GAPDH	TGATGACATCAAGAAGGTGGTGAAG	TCCTTGGAGGCCATGTGGGCCAT

analyzed using the Pearson method. The accuracy of lncRNA MIR17HG in identifying MM was evaluated using the receiver operating characteristic (ROC) analysis. The cut-off value, sensitivity, and specificity of lncRNA MIR17HG accurately diagnosing MM were determined using the Youden index [18]. The PFS and OS were displayed using Kaplan–Meier curves, and the difference of PFS and OS between groups was assessed with the logrank test. A value of $P < 0.05$ was considered statistically significant.

3. Results

3.1. Clinical Baseline Characteristics. The number of all subjects and clinical baseline data are presented in Table 2. There were no significant differences in regard to gender and age between the HC group ($N = 85$) and the MM group ($N = 108$) ($P > 0.05$). Relative to the HC group, the levels of Scr, β2-MG, LDH, calcium, immunoglobulin G (IgG), and IgA were all significantly enhanced (all $P < 0.001$), while ALB and Hb levels were reduced in the MM group ($P < 0.001$). Meanwhile, 68MM patients presented with bone lesions and 38 patients presented with renal dysfunction. Among the MM patients, 48 patients were at DS stage II and 60 patients were at DS stage III, and the number of patients at ISS stages I, II, and III were 15, 33, and 60, respectively.

3.2. MIR17HG Was Highly Expressed in Sera of MM Patients and Correlated with Clinical Stages of MM Patients. After categorizing the MM patients into different stages following DS staging and ISS, we found that Hb levels were diminished and serum calcium levels were enhanced with the progression of DS stages ($P < 0.001$, Figure 1(a)). In addition, the levels of β2-MG and LHD were augmented, while ALB level was diminished with the development of ISS stage (all $P < 0.05$, Figure 1(a)). Subsequently, the serum levels of MIR17HG in both groups were determined by means of RT-qPCR. Relative to the HC group, the serum levels of MIR17HG were markedly enhanced in MM patients ($P < 0.001$, Figure 1(b)). Moreover, the relative expression levels of serum MIR17HG in MM patients at DS stage III were markedly higher than those in patients at DS stages I-II. Similarly, there was an enhancement in serum MIR17HG levels with the development of ISS stages, and the differences were statistically significant (all $P < 0.01$, Figures 1(c) and 1(d)). Collectively, the abovementioned findings indicated that the expression of serum MIR17HG was upregulated in MM patients and further associated with the clinical stages of MM patients.

3.3. Serum MIR17HG Was Significantly Correlated with Scr, LDH, and ALB in MM Patients. Furthermore, we sought to observe the relationship between serum MIR17HG levels and clinical biochemical parameters in MM patients. Results of the Pearson analysis indicated that serum MIR17HG was correlated with Scr, LDH, and ALB in MM patients. Specifically, serum MIR17HG was markedly positively correlated with Scr and LDH in MM patients ($r = 0.5682$, $P < 0.001$; $r = 0.4331$, $P < 0.001$, Figures 2(a) and 2(b)), while also being significantly negatively correlated with ALB ($r = -0.3111$, $P = 0.0011$, Figure 2(c)).

3.4. Serum MIR17HG Had Diagnostic and Prognostic Values in MM Patients. To further elucidate the accuracy of serum MIR17HG level in MM identification, we plotted the ROC curve of MIR17HG level to distinguish MM patients from normal healthy people. The area under the curve (AUC) of MIR17HG was calculated to be 0.9349, and the cut-off value was 1.485 (sensitivity 92.59%, specificity 87.06%). These findings indicated that serum MIR17HG level >1.485 could evaluate the accuracy of MM diagnosis. In addition, patients were followed up for a total of 48 months after the treatment. According to the median serum level of MIR17HG, MM patients were categorized into the high expression group and low expression group, and the PFS and OS survival curves were drawn. According to the results of the logrank test, MM patients with high MIR17HG expression levels had prominently shorter PFS and OS than MM patients in the low MIR17HG expression group ($P < 0.01$, Figures 3(b) and 3(c)). Collectively, the abovementioned findings highlighted that the high expression of MIR17HG was associated with adverse survival of MM patients.

4. Discussion

MM represents the most common hematological cancer in the world and is further associated with an ever-increasing incidence year by year [19]. The hard-done work of our peers recently unveiled that lncRNAs are implicated in tumorigenesis, progression, metastasis, and drug resistance [20]. Additionally, evidence has come to light indicating that MIR17HG exerts a potential function in cancer biology [21]. Our findings uncovered that the serum level of MIR17HG can evaluate the accuracy of MM diagnosis and possess certain prognostic values for MM patients.

With changes ensuring in the tumor microenvironment, there can be certain biomarker and cytogenetic abnormalities present before the symptoms appear [22]. Upcoming studies have documented abnormal expression patterns of lncRNA in newly diagnosed MM patients, with lncRNA being expected to become a diagnostic and prognostic biomarker for MM [23]. One such lncRNA, namely, MIR17HG, is known to exert a potential function in cancer biology, which can promote tumorigenesis [21]. In addition, MIR17HG has been shown to promote CRC progression

Table 2: Clinical baseline data of the subjects.

	HC ($N = 85$)	MM ($N = 108$)	P
Gender (male, %)	53 (62.35%)	69 (63.89%)	0.8261
Age	54 (49, 58)	54 (50, 58)	0.4297
Biochemical indexes			
Scr (mg/dL)	0.72 ± 0.19	1.86 ± 0.41	<0.001
ALB (g/L)	42.80 ± 4.00	33.51 ± 4.08	<0.001
β2-MG (mg/L)	1.51 ± 0.33	5.88 ± 2.37	<0.001
LDH (U/L)	149.40 ± 28.33	265.10 ± 52.06	<0.001
Calcium (mg/dL)	7.86 (7.35, 8.49)	12.22 (8.92, 12.66)	<0.001
Hb (g/L)	140.50 ± 19.88	88.62 ± 25.30	<0.001
IgG (g/L)	16.50 ± 5.84	8.26 ± 3.27	<0.001
IgA (g/L)	2.03 ± 0.51	8.30 ± 3.24	<0.001
Bone lesions (cases, %)	—	68 (62.96%)	—
Renal impairment (cases, %)	—	38 (35.19%)	—
DS stage (cases, %)			
I-II	—	48 (44.44%)	—
III	—	60 (55.56%)	—
ISS stage (cases, %)			
I	—	15 (13.89%)	—
II	—	33 (30.55%)	—
III	—	60 (55.56%)	—

Notes: Scr, serum creatinine; ALB, albumin; β2-MG, β2-microglobuli; LDH, lactate dehydrogenase; Hb, hemoglobin; IgG, immunoglobulin G; IgA, immunoglobulin A; DS, Durie-Salmon; ISS, international staging system.

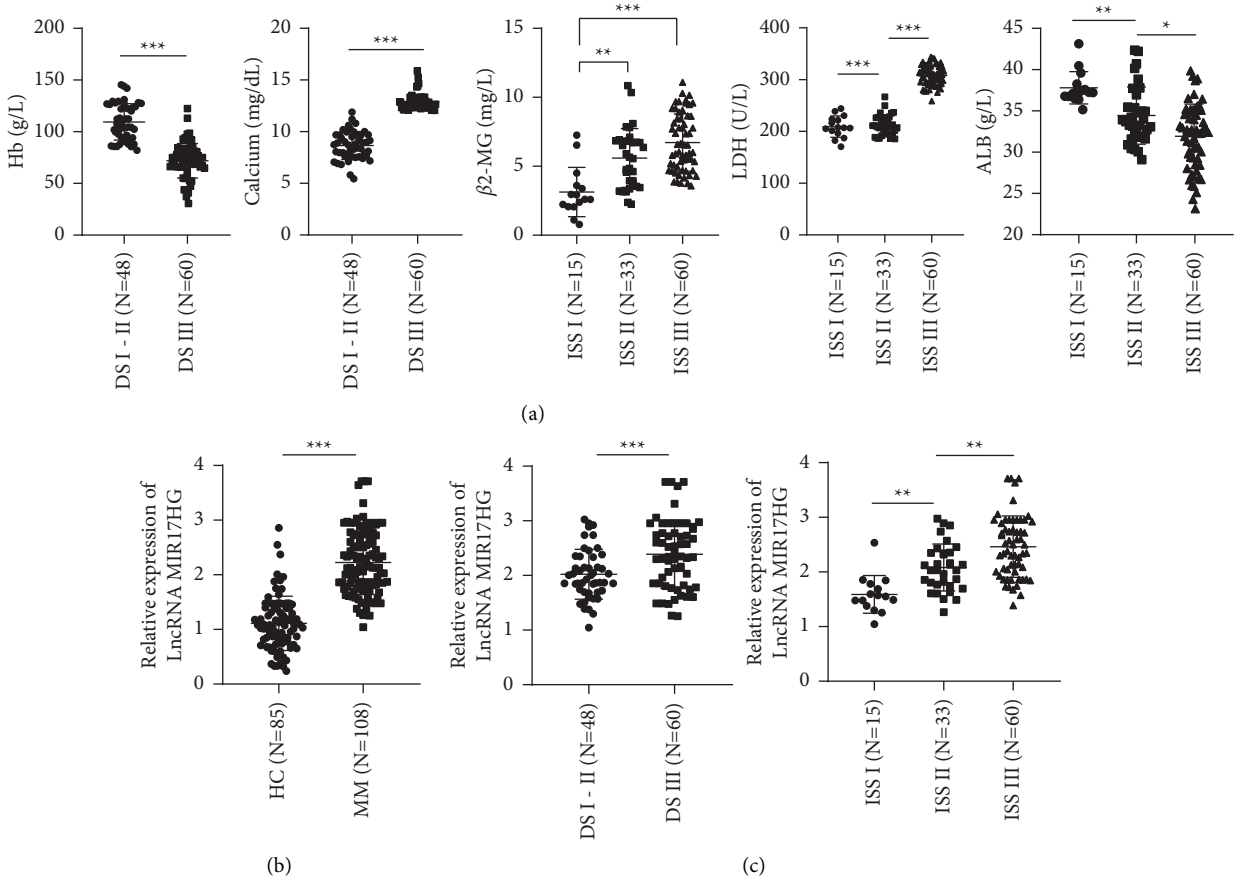

Figure 1: MIR17HG was highly-expressed in sera of MM patients and correlated with clinical stages of MM patients. (a) Measured levels of Hb, calcium, β2-MG, LDH, and ALB in MM patients at different clinical stages. (b) Measured serum levels of MIR17HG in healthy population and MM patients. (c)–(d) Measured serum levels of MIR17HG in MM patients at different clinical stages. $^{**}P < 0.01$, $^{***}P < 0.001$.

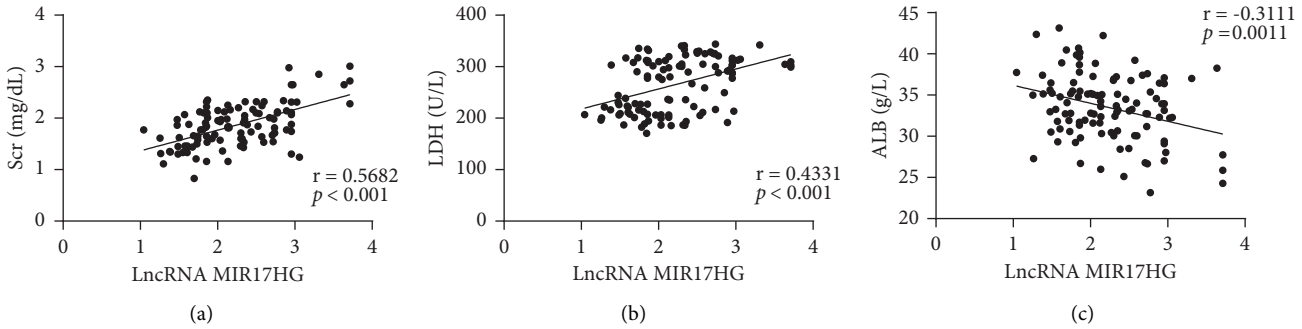

Figure 2: Serum MIR17HG was significantly correlated with Scr, LDH, and ALB in MM patients. (a)–(c) Pearson method was utilized to analyze the correlation between serum MIR17HG and Scr, LDH, and ALB in MM patients.

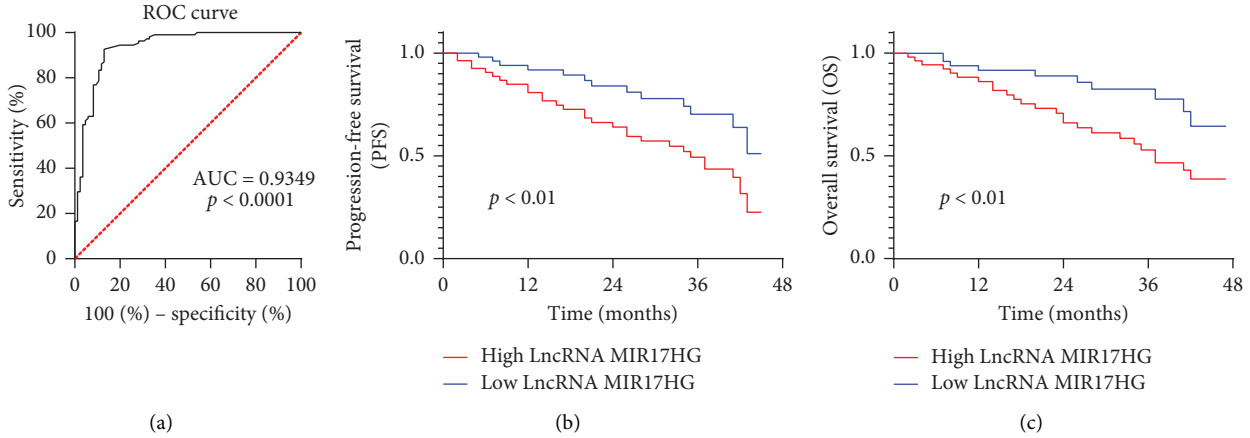

Figure 3: The serum MIR17HG exhibited diagnostic and prognostic values in MM patients. (a) ROC curve was adopted to evaluate the accuracy of serum MIR17HG level in MM diagnosis. (b) and (c) The PFS and OS of MM patients with high and low levels of MIR17HG were plotted by Kaplan–Meier curves.

through miR-17-5p [24]. Further adding to its importance, MIR17HG can also promote the proliferation, migration, and invasion of retinoblastoma cells through up-regulating HIF-1α expression by sponging miR-155-5p [25]. To the best of our knowledge, our study is the first of its kind to demonstrate a considerable increase in serum MIR17HG levels in MM patients. Similarly, MIR17HG protein expression levels in meningiomas are higher than those in normal meningeal tissues [10], which further supports our findings. Additional experimentation in our study revealed that the contents of clinical detection indexes Scr, β2-MG, LDH, calcium, IgG, and IgA were discernibly raised, while the contents of Hb and ALB were markedly lowered in MM patients, which are indicative of greater disease consumption and tumor burden. Furthermore, a vast proportion of the MM patients had bone lesions and some patients presented with renal impairment. Additionally, we uncovered that serum MIR17HG was positively correlated with Scr and LDH and negatively correlated with ALB in MM patients, emphasizing that the high expression of MIR17HG was associated with poor general disease status in MM patients. Some lncRNAs including genes such as MIR17HG are promising for the diagnosis and prognosis of colon adenocarcinoma [26]. More importantly, we also learnt that the AUC of MIR17HG expression to evaluate the accuracy of identifying MM was 0.9349, with a cut-off value of 1.485. Consistently, the expression of MIR17HG was upregulated in the sera of alopecia patients, and the ROC curve revealed that MIR17HG possessed a high value in distinguishing patients from controls (AUC = 0.85) [27]. Collectively, the abovementioned findings and evidence make it plausible to conclude that serum MIR17HG level >1.485 could evaluate the accuracy of MM diagnosis.

MM is a highly heterogeneous disease, and the prognosis of MM patients varies greatly [28]. Accordingly, the accurate estimation of the survival time of MM patients remains a major challenge [29]. DS and ISS are well-known prognostic tools, which stratify newly diagnosed MM patients into different risk groups based on widely used serum markers (such as ALB, β2-MG, and LDH) and represent a critical modality in predicting the survival of MM patients at diagnosis [30]. The genetic variants in MIR17HG also exert a significant impact on the prognosis of glioma and susceptibility of head and neck squamous cell carcinoma in Chinese Han populations [31, 32]. Moreover, we unraveled that MM patients at DS stage III possess higher serum MIR17HG expression levels than those at DS stages I-II, and the serum MIR17HG levels exhibited an increase with the development of ISS stages. In parallel, the study performed by Shen et al. revealed that lncRNA AL928768.3 is highly

expressed in MM samples and cell lines and further substantially correlated with ISS stages [33]. It is reasonable to conclude that the high expression of MIR17HG in sera of MM patients is associated with later clinical stages in MM patients.

Accumulating studies have shed light on the potency of several specific lncRNAs as prognostic indicators in MM patients [34, 35]. In particular, high expression levels of MIR17HG were previously associated with poor PFS and OS in CRC patients [13]. Likewise, our findings revealed that MM patients with high MIR17HG expression had significantly shorter PFS and OS than those with low MIR17HG expression. In light of the fact that MIR17HG is associated with higher Scr, LDH levels, and more advanced clinical stages, which are associated with poorer survival of MM patients [36], it is not difficult to infer that the high MIR17HG expression is associated with adverse survival of MM patients.

In conclusion, findings uncovered in our study elucidated that serum MIR17H can aid the evaluation of accurate MM diagnosis, and high levels of serum MIR17H can predict poor prognosis of MM patients. However, there are certain limitations to our study. First, MM is a heterogeneous disease with complex molecular biological characteristics [37]. In MM, some cytogenetic abnormalities including *t* (4; 12), *t* (14; 16), and del (17p) are highly risky and are also associated with worse prognosis [38, 39]. However, we were unable to provide corresponding results and thus failed to analyze the correlation of lncRNA MIR17HG with cytogenetics, which is a major limitation of the study. Second, the comparatively small sample size may be subjected to the selection bias, which limits the generalizability of our findings. In addition, the detailed mechanism of MIR17HG in MM has not been clarified. Finally, the MIR17HG expression was measured only before the treatment, and no further determination was performed after the treatment. In future studies, a larger cohort of patients recruited from multiple hospitals will be studied to reduce the bias. Moreover, we need to further explore the underlying mechanism by which MIR17HG affects MM development and the changes in MIR17HG levels after the treatment.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical Approval

The current study was approved by the Academic Ethics Committee of Bozhou People's Hospital (Approval number: bzzc2021023). All experimental procedures were strictly implemented according to the Declaration of Helsinki.

Consent

Signed informed consents were obtained from all participants prior to enrollment.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

HFG is the guarantor of integrity of the entire study and contributed to the study concepts, definition of intellectual content, and experimental studies and edited and reviewed the manuscript. HLC contributed to the study design. JZF contributed to the literature research, statistical analysis, and data analysis and drafted the manuscript. SEL contributed to the clinical studies and data acquisition. All authors read and approved the final manuscript.

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