Clinical significance of miR-372 and miR-495 in acute myeloid leukemia

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Abstract. The present study aimed to explore the clinical significance of miR-372 and miR-495 in acute myeloid leukemia (AML). Eighty-one AML patients (research group) admitted to the First Hospital of Lanzhou University from March 2012 to January 2014 were selected, and 60 healthy persons (control group) were selected. The expression levels of miR-372 and miR-495 in the peripheral blood of the subjects were detected by reverse transcriptase quantitative PCR, and their diagnostic and prognostic values in AML were analyzed. The miR-372 expression level in the peripheral blood of patients in the research group was significantly higher than that in the control group (P<0.05), and the miR-495 level was significantly lower than that in the control group (P<0.05). The area under the curve (AUC), sensitivity, and specificity of miR-372 combined with miR-495 in the diagnosis of AML were 0.925, 86.43, and 93.33% respectively. The 5-year survival rate of patients with high expression of miR-372 was lower than that of those with low expression of miR-372 (P<0.05), and the 5-year survival rate of patients with high expression of miR-495 was higher than that of those with low expression of miR-495 (P<0.05). miR-372 and miR-495 were independent risk factors for the prognosis and survival of AML patients. miR-372 expression increased in AML, while miR-495 decreased. miR-372 and miR-495 are effective indicators for the early diagnosis and prognosis of AML.

Introduction

Acute myeloid leukemia (AML) is characterized by the dysfunction of differentiation and maturation of bone marrow precursor cells, leading to damage or even loss of normal hematopoietic function and poor prognosis (1). With an aging population worldwide, the morbidity of AML is increasing, and the recurrence rate of AML is high. In the United States, 21,000 new AML patients are diagnosed each year, of which approximately 10,000 succumb to the disease; moreover, the mortality rate of patients over 65 years of age is higher than 90% (2,3). Thus, the identification of biological indicators closely related to AML is quite significant for the early diagnosis and prognosis of AML patients.

Bone marrow aspiration cytology is still the gold standard for AML, but this method is more traumatic, especially in young AML patients. MicroRNAs (miRNAs) are small non-coding RNAs found in eukaryotes, which can form a complex biological process control network and participate in life activities, including the occurrence of cancer (4,5). In recent years, many studies have reported that miRNAs are closely related to AML, which are not only possible novel markers for the diagnosis and prognosis of AML, but also potential therapeutic targets (6). Studies have found that miRNAs play a vital role in almost all aspects of AML disease progression, including cell proliferation and differentiation (7). Zhao *et al* (8) discovered that the plasma miR-372 level in AML patients was significantly upregulated, and tumor-suppressor gene PTEN was targeted to inhibit the migration and cloning of tumor cells. In addition, miR-495 was found to be down-regulated in AML and ectopic expression of miR-495 greatly inhibited the activity of tumor cells and increased apoptosis (9). Nevertheless, the significance of miR-372 and miR-495 in the diagnosis and prognosis of AML has not been reported.

The clinical significance of miR-372 and miR-495 in AML may provide guidance for clinical AML diagnosis and patient prognosis.

Patients and methods

Research subjects. From March 2012 to January 2014, 81 AML patients (research group) and 60 healthy subjects (control group) aged 20-65 years were enrolled at The First Hospital of Lanzhou University. Inclusion criteria precluded that all patients were diagnosed with AML by bone marrow puncture needle aspiration cytology and presented with primary AML; the medical records and follow-up data were complete; the survival time of prognosis was more than 2 months, and there were no

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pregnant or lactating women included. Those subjects in the control group had no clinicopathological symptoms or history of cancer. Exclusion criteria were as follows: Patient survival was less than 2 months; patients receiving previous bone marrow transplantation; patients presenting with other tumors and blood diseases, severe liver and kidney insufficiency, systemic infectious diseases, immune diseases and mental and communication disorders. This study conformed to the Helsinki Declaration and was approved by the Ethics Committee of The First Hospital of Lanzhou University (Lanzhou, Gansu, China). All subjects were consulted by telephones or mails, and an informed consent was signed by all subjects.

Acquisition of information. Sex, age, FAB typing, white blood cell count, hemoglobin, platelets, the proportion of peripheral blood immature cells, the proportion of bone marrow immature cells, chromosome typing, karyotype, CD34, CD56 and gene mutation of patients were extracted from the patient medical records.

Collection of peripheral blood. The nurses in our hospital collected the peripheral blood of the subjects through vacuum venous blood collection. The blood was sent for examination within 1 h after the completion of blood collection.

Observation indicators. The expression levels of miR-372 and miR-495 in the peripheral blood of the included subjects were detected using reverse transcriptase quantitative PCR (RT-qPCR), and their diagnostic and prognostic value in regards to AML were analyzed. Risk factors affecting the prognosis and survival of AML patients were assessed via Cox regression analysis. Peripheral blood was collected in the early morning when subjects had an empty stomach.

RT-qPCR. Peripheral blood of all subjects was collected, and total RNA was extracted from the cells using TRIzol lysate (Guangzhou Lanji Biotechnology Co., Ltd.). The extraction procedure was carried out according to the instructions of the kit. The concentration and purity of the extracted RNA were analyzed by micro-ultraviolet spectrophotometer DanoProp 1000 (Thmorgan Biotechnology Co., Ltd.). The A260/A280 value was between 1.8 and 2.1, which was considered to meet the experimental requirements. The integrity of RNA was analyzed by 3% agarose gel electrophoresis (Gel Electrophoresis kit; Shanghai Jingke Chemical Technology Co., Ltd.). RT-qPCR reaction was conducted after RNA extraction. The reverse transcription reaction system was as follows: 5X TransScript® All-in-One Superfix for PCR (4 μl; TransGen Biotech, China), total RNA (2 μg), ribonuclease-free distilled water added to 20 μl; 25˚C for 10 min, 42˚C for 30 min, deactivation of reverse transcriptase at 85˚C for 5 sec. The reaction was terminated. The PCR amplification system was as follows: cDNA template (2 μl), 2X TransTaq® High Fidelity (HiFi) PCR SuperMix II (25 μl; TransGen Biotech, China), upstream primer and downstream primer 1 μl each, double-distilled water added to 50 μl. Afterward pre-denaturation was carried out at 95˚C for 3 min, 94˚C for 2 min, 94˚C for 30 sec, 55˚C for 30 sec, 72˚C for 1-2 kb/min, for a total of 42 cycles, and extension was carried out at 72˚C for 5 min after the completion of cycles. U6 was used as the reaction internal reference and the results were analyzed by $2^{-\Delta Cq}$ (10). The primer sequences were designed and synthesized by Hepeng (Shanghai) Biotechnology Co., Ltd. More details are shown in Table I.

Statistical analysis. SPSS 19.0 (Asian Analytics formerly SPSS, China) was applied. All measurement data are expressed as mean ± standard deviation (SD). The comparison between two groups was conducted by independent-samples t-test. Receiver operating characteristic (ROC) analysis was used to analyze the diagnosis of miR-372 and miR-495 in AML. Kaplan-Meier (K-M) curve was used to analyze the relationship between miR-372, miR-495 and the 5-year survival rate of AML patients, and the log rank test was used for variance analysis. COX regression was used to analyze the risk factors affecting the prognosis and survival of AML patients. A P-value less than 0.05 was considered to indicate statistical significance.

Results

Demographical data. Eighty-one subjects were included in the research group, including 43 males and 38 females with a mean age of 42.37±10.13 years. Sixty subjects were included in the control group, including 40 males and 20 females with a mean age of 40.72±8.63 years. There was no statistical difference in the sex ratio (P=0.105) and age (P=0.359) between the two groups. Other basic data of patients in the two groups are shown in Table II.

Expression levels of miR-372 and miR-495 in AML. The miRNA level was tested by RT-qPCR. The miR-372 level in peripheral blood of patients in the research group was significantly higher than that in the control group, and the miR-495 level was significantly lower than that in the control group (P<0.05) (Fig. 1).

Diagnostic value of miR-372 and miR-495 in AML. The area under the curve (AUC), cut-off value, sensitivity, and specificity of miR-372 in the diagnosis of AML were 0.853, 1.150, 87.65, and 75.00%, respectively. The AUC, cut-off value, sensitivity, and specificity of miR-495 in the diagnosis of AML were 0.824, 2.097, 65.43, and 91.67%, respectively. The AUC, sensitivity and specificity of miR-372 combined with miR-495 in the diagnosis of AML were 0.925, 86.43, and 93.33%, respectively (Fig. 2).

Association between miR-372, miR-495, and the 5-year survival rate of AML patients. Using the cut-off value as the critical value, values equal or greater than the cut-off value was used to designate patients in a high expression group and values less than the cut-off value were used to designate patients to a low expression group. K-M curve analysis results revealed that the 5-year survival rate of patients with high expression of miR-372 was lower than that of patients with low expression of miR-372 (P=0.013) (Fig. 3A), and the 5-year survival rate of patients with high expression of miR-495 was higher than that of patients with low expression of miR-495 (P=0.007) (Fig. 3B).

Risk factors for survival and prognosis of AML patients. COX regression analysis showed that white blood cell count

Table I. Primer sequences for RT-qPCR.

Variable	Forward primer	Reverse primer
miR-372	5'-ACACTCCAGCTGGGAAAAGCTGGGTTGAGA-3'	5'-TGGTGTCGTGGAGT-3'
miR-495	5'-TCCGATTCTTCACGTGGTAC-3'	5'-GTGCAGGGTCCGAGGT-3'
U6	5'-GCGCGTCGTGAAGCGTTC-3'	5'-GTGCAGGGTCCGAGGT-3'

Table II. Demographical data and biochemical parameters.

Data/parameters	Research group (n=81)	Control group (n=60)	χ^2/t	P-value
Sex, n (%)			2.625	0.105
Male	43 (53.09)	40 (66.67)		
Female	38 (46.91)	20 (33.33)		
Age (years)	42.37±10.13	40.72±8.63	0.921	0.359
FAB typing, n (%)				
M1	5 (6.17)			
M2	28 (34.58)			
M3	13 (16.05)			
M4	14 (17.28)			
M5	19 (23.46)			
M6	1 (1.23)			
M7	1 (1.23)			
White blood cell count ($x10^9$/l)	57.76±9.08	4.62±1.03	45.077	<0.001
Hemoglobin (g/l)	54.37±10.28	101.75±8.45	29.139	<0.001
Platelets ($x10^9$/l)	48.73±9.82	135.63±12.64	45.943	<0.001
Proportion of immature cells in peripheral blood	44.84±9.24	Negative		
Proportion of immature cells in bone marrow	68.98±15.20			
Chromosome typing, n (%)				
Low-risk group	16 (19.75)			
Non-low-risk group	65 (80.25)			
Karyotype, n (%)				
Normal	19 (23.46)			
t (8:21)	23 (28.40)			
t (15:17)	11 (13.58)			
11q23	8 (9.88)			
inv (16)	9 (11.11)			
Rests	11 (13.58)			
CD34 (+/-)	37/44			
CD56 (+/-)	39/42			
Gene mutation				
c-KIT (+/-)	12/69			
CEBPA (+/-)	13/68			
FLT3-ITD (+/-)	7/74			
FLT3-TKD (+/-)	3/78			
Negative (+/-)	46/35			

(P=0.009), proportion of immature cells in peripheral blood (P=0.022), chromosome typing (P=0.024), gene mutation (P=0.028), miR-372 (P=0.016), and miR-495 (P=0.017) were independent risk factors for the prognosis and death of AML patients (Tables III and IV).

Discussion

At present, the pathogenesis of AML has not been fully studied. Since gene mutations often occur in AML patients and their prognosis is also variable, the identification of

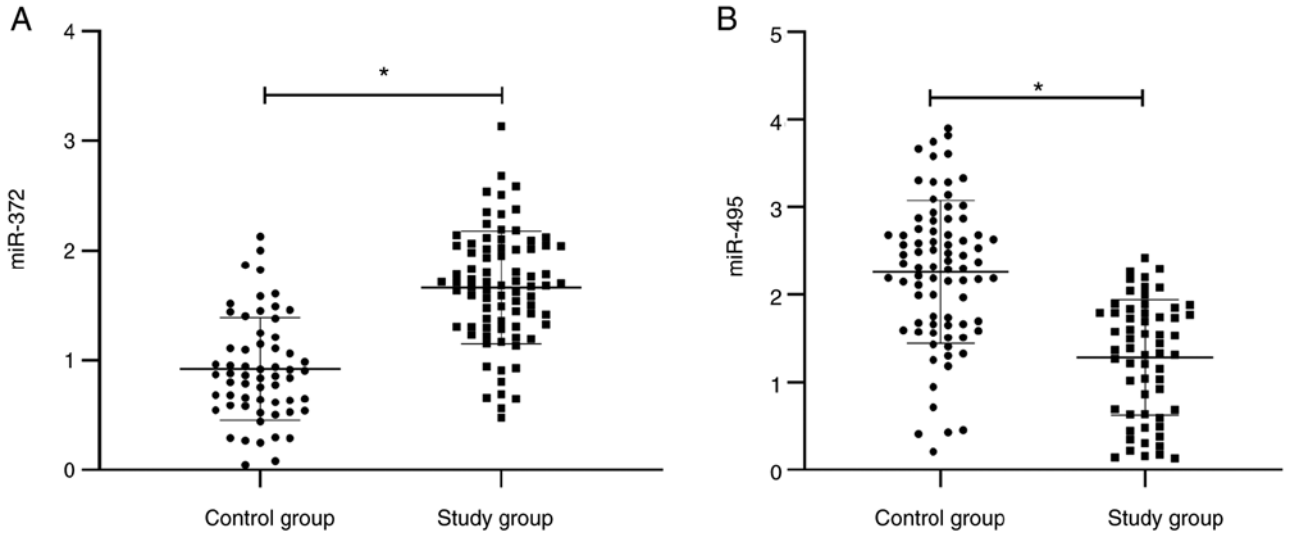

Figure 1. Expression of miR-372 and miR-495 in AML. (A) RT-qPCR showed that the miR-372 level was higher in the study group when compared with that in the control group. (B) The miR-495 level in the AML patient (study) group was lower than that in the control group. *P<0.05. AML, acute myeloid leukemia.

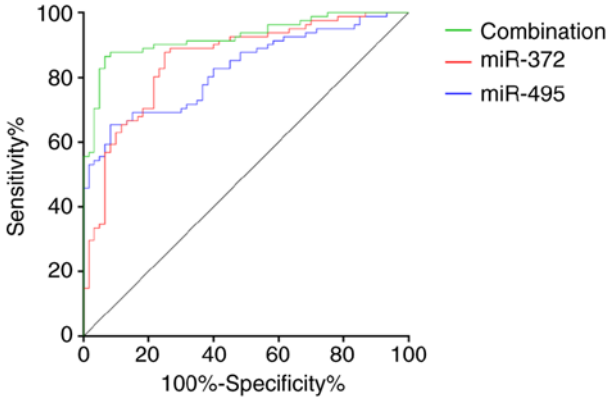

Figure 2. Diagnostic value of miR-372 and miR-495 in AML. AUC of the combined values for miR-372 and miR-495 for diagnosis was higher than that of each single miRNA. The AUC, sensitivity and specificity of miR-372 combined with miR-495 were 0.925, 86.43 and 93.33%, respectively. AML, acute myeloid leukemia; AUC, area under the curve.

accurate indicators for prognosis and early diagnosis of AML is quite significant to guide the clinical treatment of AML and improve the prognosis of patients.

The present study analyzed the clinical significance of the miR-372 and miR-495 expression levels in AML. The research results showed that, consistent with the results reported in previous studies, the miR-372 expression in peripheral blood of patients with AML increased while the miR-495 expression decreased (8,9). Then, the diagnostic value of miR-372 and miR-495 in AML was analyzed. At present, there are few reports on the diagnosis of miRNAs in AML. Wang *et al* (11) reported the diagnostic value of miR-29a and miR-142-3p in 52 AML patients and 100 healthy adults. Their research results showed that the AUC of miR-29a combined with miR-142-3p in the diagnosis of AML could reach 0.97, and the sensitivity and specificity were 90 and 100%, respectively. This study signified that the AUC of miR-372 combined with miR-495 in 81 AML patients and 60 healthy subjects was 0.925, and the sensitivity and specificity were 86.43 and 93.33% respectively, which were slightly lower than those of Wang *et al*. Ohyashiki *et al* (12) reported that the AUC of miR-92a in 91 AML patients and 25 healthy subjects was 0.9959, while Yan *et al* (13) indicated that the AUC of miR-217 in 89 AML patients and 60 healthy adults was 0.836, with sensitivity and specificity of 74.16 and 83.33% respectively. Differences between the results of these research studies were not only caused by different miRNAs, but also caused by different sample sources and sample sizes. We will further carry out multi-center clinical research verification.

The research results on the prognostic relationship between miR-372, miR-495, and AML patients showed that the 5-year survival rate of patients with high miR-372 expression was lower than that of patients with low miR-372 expression, while the 5-year survival rate of patients with high miR-495 expression was higher than that of patients with low miR-495 expression. In many studies, it has been reported that miR-372 and miR-495 can affect a variety of biological behaviors of tumor cells, such as modulating miR-372 to inhibit proliferation and invasion of renal cancer cells (14). Up-regulating miR-372 was also found to promote the migration of squamous cell carcinoma cells in the head and neck by downregulating p62, and the expression of miR-372 was also found to be up-regulated in a hypoxic environment, promoting the progression of squamous cell carcinoma in the head and neck (15). miR-495 was reported to have similar results. Mao *et al* (16) reported that miR-495 could inhibit proliferation, migration, and invasion of esophageal cancer cells. Chen *et al* (17) reported that miR-495 demethylation could inhibit the invasion of breast cancer cells and promote their apoptosis. These functions of miR-372 and miR-495 are key factors affecting the prognosis of cancer patients. Yu *et al* (18) confirmed that miR-372 was a biomarker for the diagnosis and prognosis of patients with early colorectal cancer. Wang *et al* (19) verified that miR-495 was a prognostic factor for medulloblastoma. The results of this study also showed that, similar to the previously reported results, age, white blood cell count, proportion of immature cells in peripheral blood, chromosome typing, and gene

Table III. Results of the COX univariate analysis.

Variables	B	SE	Wald	df	Sig.	Exp (B)	95% CI Exp (B)	
							Lower part	Upper part
Sex	-0.158	0.326	0.234	1	0.628	0.854	0.450	1.619
Age (years)	0.075	0.017	20.687	1	<0.001	1.078	1.044	1.114
FAB typing	-0.021	0.115	0.034	1	0.854	0.979	0.782	1.226
White blood cell count	0.051	0.018	8.445	1	0.004	1.052	1.017	1.089
Hemoglobin	-0.036	0.015	5.841	1	0.016	0.964	0.936	0.993
Platelet	-0.007	0.017	0.188	1	0.665	0.993	0.960	1.027
Proportion of immature cells in peripheral blood	0.066	0.017	15.77	1	<0.001	1.068	1.034	1.104
Proportion of immature cells in bone marrow	0.009	0.01	0.719	1	0.396	1.009	0.988	1.030
Chromosome typing	-2.132	0.359	35.191	1	<0.001	0.119	0.059	0.240
Karyotype	-0.141	0.096	2.127	1	0.145	0.869	0.719	1.050
CD34	-0.203	0.325	0.391	1	0.532	0.816	0.432	1.542
CD56	-0.401	0.327	1.511	1	0.219	0.669	0.353	1.269
Gene mutation	-0.363	0.096	14.179	1	<0.001	0.696	0.576	0.840
miR-372	0.953	0.229	17.339	1	<0.001	2.594	1.656	4.064
miR-495	-0.615	0.172	12.731	1	<0.001	0.541	0.386	0.758

B, covariate coefficient; SE, standard error; Wald, Wald Chi-square; DF, degree of freedom; sig, probability p; Exp (B), relative risk; 95% CI Exp (B), 95% confidence interval of OR value.

Table IV. Results of the COX multivariate analysis.

Variables	B	SE	Wald	df	Sig.	Exp (B)	95% CI Exp (B)	
							Lower part	Upper part
Age (years)	0.029	0.022	1.776	1	0.183	1.029	0.986	1.074
White blood cell count	-0.015	0.024	0.359	1	0.009	2.986	0.940	4.034
Hemoglobin	0.003	0.027	0.016	1	0.901	1.003	0.952	1.057
Proportion of immature cells in peripheral blood	0.063	0.028	5.232	1	0.022	1.065	1.009	1.124
Chromosome typing	-1.728	0.41	17.773	1	0.024	0.178	0.080	0.397
Gene mutation	-0.251	0.114	4.831	1	0.028	0.778	0.622	0.973
miR-372	0.484	0.358	1.828	1	0.016	1.623	0.804	4.273
miR-495	-0.168	0.297	0.322	1	0.017	2.845	0.472	4.511

B, covariate coefficient; SE, standard error; Wald, Wald Chi-square; DF, degree of freedom; sig, probability p; Exp (B), relative risk; 95% CI Exp (B), 95% confidence interval of OR value.

mutation were independent risk factors for prognosis and survival of AML patients (20-23). It was found in this study that miR-372 and miR-495 were also independent risk factors for the prognosis and survival of AML patients, which were rarely reported in AML. Gu *et al* (24) confirmed that high expression of miR-372 was an independent predictor for poor prognosis of patients with liver cancer, and there had been few such reports on miR-495. However, this also improved the credibility of our research results to a certain extent.

There may be some limitations in this study. Invasive fungal infection and bone marrow failure are also factors affecting the prognosis of AML (25,26). Because of genetic abnormality, some AML patients with t (8; 21) (q22; q22.1) mutations have a good prognosis; therefore, the relationship between miR-372, miR-495 and AML should be further analyzed on the basis of the prognosis of patients; in addition, different AML subtypes have different treatment plans, thus we need to further analyze the clinical significance of miR-372 and miR-495 expression

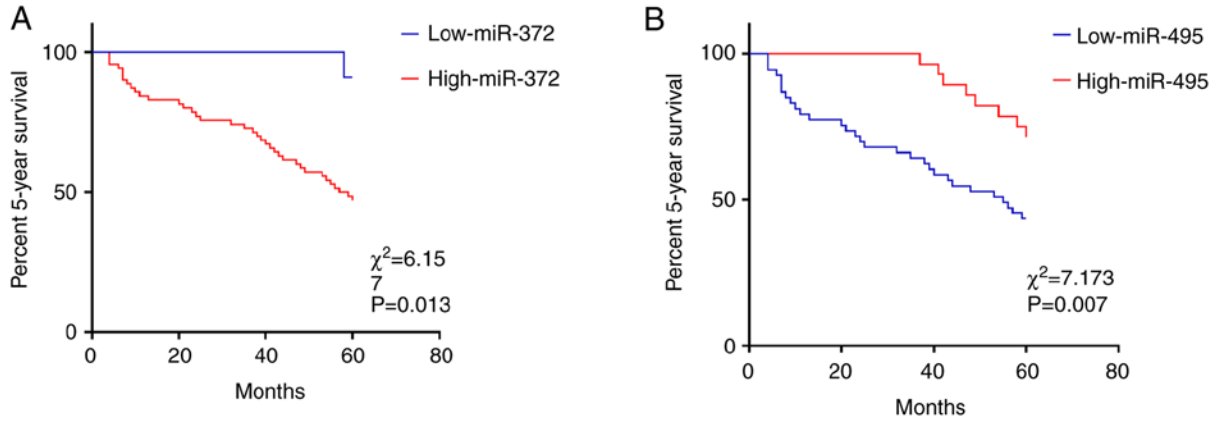

Figure 3. Relationship between miR-372, miR-495, and the 5-year survival rate of AML patients. (A) Association between miR-372 and the 5-year survival rate in patients with AML. (B) Association between miR-495 and the 5-year survival rate in patients with AML. The 5-year survival rate of patients with high expression of miR-372 was lower than that of those with low expression, while that of patients with high expression of miR-495 was higher than that of those with low expression.

in AML subtypes, However, the data collected in this study were insufficient. We will continue to deepen our research and supplement more comprehensive results. What's more, we also need to further analyze the mechanisms of miR-372 and miR-495 in AML, which require more research verification.

In conclusion, miR-372 was expressed higher in AML patient peripheral blood samples, while miR-495 was expressed lower. miR-372 and miR-495 may be effective indicators for the early diagnosis and prognosis of AML.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

WZ conceived the study and wrote the manuscript. BW performed the PCR analysis. BL analyzed and interpreted the patient data. SW and LZ conducted the statistical analysis. All authors read and approved the manuscript and agree to be accountable for all aspects of the research in ensuring that the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of The First Hospital of Lanzhou University (Lanzhou, Gansu, China). Patients who participated in this research, signed the informed consent and had complete clinical data. Signed written informed consents were obtained from all the patients and/or their guardians.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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