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Expression of the miR-148/152 Family in Acute Myeloid Leukemia and its Clinical Significance

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF Xiao-Xue Wang
DF Rui Zhang
AG Yan Li

Department of Hematology, The First Hospital, China Medical University, Shenyang, Liaoning, P.R. China

Corresponding Author: Yan Li, e-mail: liyan2@medmail.com.cn
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Background: MicroRNAs (miRNAs) play an important role in the development and progression of acute myeloid leukemia (AML). The miR-148/152 family has been reported to be express differently in various kinds of tumors. We investigated the expression level of the miR-148/152 family in AML patients and their clinical significance.

Material/Methods: Expression levels of the miR-148/152 family in 80 patients with newly diagnosed AML and 20 healthy participants were analyzed by qRT-PCR. We also evaluated the relationship between the expression levels of the miR-148/152 family and clinicopathological features of AML patients.

Results: Compared with healthy controls, we found a significant lower expression of downregulated miR-148/152 in AML patients ($p<0.0001$). The expression of miR148/152 family was associated with various AML clinicopathological risk parameters including FAB classifications, cytogenetics, and gene mutations. The number of patients with high expression levels of miR-148a/b was significantly increased in the low-risk group and significantly decreased in the high-risk group. ($p=0.025$, $p=0.000$, respectively). Patients with higher expression of miR-148b showed a higher complete remission (CR) rate ($p=0.043$). Importantly, higher expression of miR-148a/b was correlated with lower relapse rate ($p=0.035$, $p=0.027$, respectively) and showed a longer relapse-free survival (RFS) ($p=0.0321$, $p=0.002$, respectively). In the subgroup analysis, RFS was significantly affected by the expression of miR-148a/b in patients the high and the intermediate-risk groups ($p=0.0499$, $p=0.0114$, respectively).

Conclusions: The expression levels of the miR-148/152 family were lower in patients with AML compared to healthy controls, and were associated with various AML clinicopathological parameters and therapeutic effect. The miR-148/152 family may prove to be a new biomarker for AML.

MeSH Keywords: Leukemia, Promyelocytic, Acute • MicroRNAs • Recurrence • Survival Analysis

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Background

Acute myeloid leukemia (AML) is a hematological malignancy characterized by abnormal clonal proliferation and arrested differentiation of myeloid precursors. Leukemic blasts accumulate in the bone marrow, peripheral blood, and other tissues, resulting in greater reductions of normal blood cells [1]. Recurring chromosomal aberrations and gene mutations contribute to the pathogenesis of AML. Although good progress has been made in the field of pathogenesis and therapeutic strategies, it is still difficult to achieve long-term survival for all patients and to predict clinical outcome for individuals [2,3]. MiRNAs are a set of small, single-stranded, endogenous, noncoding RNAs which negatively regulate gene expression by binding to the mRNAs of protein-coding genes, thereby degrading or blocking their translation [4–6]. Moreover, as oncogenes or tumor suppressor genes, miRNAs have been reported to be involved in various tumorigenic processes such as cell proliferation, apoptosis, and angiogenesis [7]. An increasing number of studies have found that miRNAs may be potential biomarkers in the diagnosis and prognosis of AML [8,9]. miR-148a, miR-148b, and miR-152 are three members of the miR-148/152 family with similar sequences, structures, and the same seed region [10]. All three members have been shown to be downregulated/upregulated in many different types of tumors (e.g., gastrointestinal, ovarian, hepatocellular carcinoma, and pancreatic cancer). Several studies have indicated that members of the miR-148/152 family are expressed differentially in hematological malignancies such as acute lymphoblastic leukemia, multiple myeloma, and lymphoma [11–14]. However, few studies have specifically focused on the entire miR-148/152 family regarding expression features and relationship with clinical characteristics in patients with AML. In the present study, we investigated the expression of the entire miR-148/152 family in bone marrow samples from patients with AML and in healthy controls. In addition, we discuss the associations between the expression levels of the miR-148/152 family and the clinical parameters of AML, which may help us develop a better understanding of AML.

Material and Methods

Study population

This study was carried out between June 2014 and March 2015. In total, 80 patients with newly diagnosed AML (median age, 45 years; range, 18–68 years; female-to-male ratio, 2: 3) and a control group of 20 healthy participants were recruited from The First Hospital of China Medical University, Shenyang, People's Republic of China. People enrolled in this study did not have any history of tumor disease and did not receive any anti-tumor drugs. The diagnosis and classification of AML patients were based on French-America-British (FAB) and World Health Organization criteria [15,16]. All AML patients, except for those with AML M3 subtype, were treated with standard-dose cytarabine 100 mg/m^2 continuous infusion for seven days in addition to idarubicin 8 mg/m^2 or daunorubicin 60 mg/m^2 for three days. Patients were assessed for response on the 28th day of the first chemotherapy cycle. Complete remission (CR) was defined by <5% blast cells in the bone marrow and normalization of the peripheral blood counts at four weeks after starting induction therapy, as well as no residual evidence of extramedullary disease. Relapse following CR was defined as reappearance of leukemic blasts in the peripheral blood or the finding of more than 5% blasts in the bone marrow not attributable to other causes. Relapse-free survival (RFS) referred to the time from CR to relapse. Overall survival (OS) was measured from the day of diagnosis until death from any cause [2].

Sampling of bone marrow

The Ethics Committee of The First Hospital of China Medical University approved this study. All patients signed informed consent before bone marrow puncture. Diagnosis, as well as chromosomal aberrations and molecular aberrations, were identified using standard procedures for bone marrow morphology, cytochemistry, flow cytometry, DNA sequencing technology, karyotype analysis, and/or FISH. Mononuclear cells were isolated by Ficoll-Hypaque density gradient centrifugation of 3 mL bone marrow samples.

Extraction of total RNA and reverse transcription

Total RNA was extracted using RNAiso Plus (Takara), according to the manufacturer's protocol. The quantity and concentration of RNA were spectrophotometrically assessed by measuring absorbance at A260/280. Then total RNA was polyadenylated with adenosine triphosphate by *Escherichia coli* poly (A) polymerase at 37°C for 30 minutes, following the manufacturer's protocol for a Poly (A) Tailing Kit (Thermo). Then, 5 μg total miRs was used as a template into synthesis of cDNA using M-MLV Reverse Transcriptase (Promega) in accordance with the manufacturer's instructions to obtain cDNA; the cDNA was subsequently held at –20°C. Individual reactions were carried out in a total volume of 19 μL using thermal condition: 75°C for 10 minutes, 37°C for 50 minutes, and 70°C for 15 minutes.

Real-time polymerase chain reaction

Quantitative real-time (RT)-PCR was run on an ABI 7500 Real-Time PCR System (ABI) using SYBR Green PCR Mix (Takara). The reaction was incubated in a 96-well optical plate using 40 amplification cycles of 95°C for 35 seconds, 60°C for 34 seconds, 95°C for 15 seconds, 60°C for 60 seconds, 95°C for 15 seconds, and 60°C for 15 seconds. Primer sequences used for real-time analysis are shown in Table 1. The relative expression

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Table 1. Primers for quantitative RT-PCR.

Primers for quantitative RT-PCR	
miR-148a F	TCAGTGCACTACAGAACTTTGT
miR-148a R	GCTGTCAACGATACGCTACGT
miR-148b F	TCAGTGCATCACAGAACTTTGTAA
miR-148b R	GCTGTCAACGATACGCTACGT
miR-152 F	TCAGTGCATGACAGAACTTGGAA
miR-152 R	GCTGTCAACGATACGCTACGT
U6 F	CGCTTCGGCAGCACATATAC
U6 R	TTCACGAATTTGCGTGTCAT

of miR-148/152 family was calculated by the comparative $2^{-\Delta\Delta Ct}$ method using U6 small nuclear RNA levels as internal control.

Statistical analysis

Comparisons of the miR-148/152 family expression levels between AML patients and healthy control group were estimated using the Mann-Whitney U test (for independent samples). With regard to the association of AML clinicopathological risk parameters with miR-148/152 expression levels, comparisons of continuous variables were tested with Mann-Whitney U test while categorical variables were analyzed with the two-tailed χ^2 test or Fisher's exact test (expected frequency <5). Comparisons among three or more groups were performed with Kruskal-Wallis One-Way ANOVA analysis. The Spearman correlation coefficient was used for correlation analysis of expression levels of the three miR-148/152 family members. Survival and relapse were plotted with Kaplan-Meier curves and differences were tested using the log-rank test. Results were considered statistically significant at $p<0.05$. All statistical analyses were performed with SPSS 17.0 software and GraphPad Prism 5.

Results

Decreased expression of the miR-148/152 family in AML patients

To examine whether the miR-148/152 family members were abnormally expressed in AML, we performed qRT-PCR to detect their levels in bone marrow mononucleic cells taken from AML patients and healthy controls. The expression levels of all the miR-148/152 members were significantly decreased in AML patients compared with the healthy controls ($p<0.0001$, Figure 1).

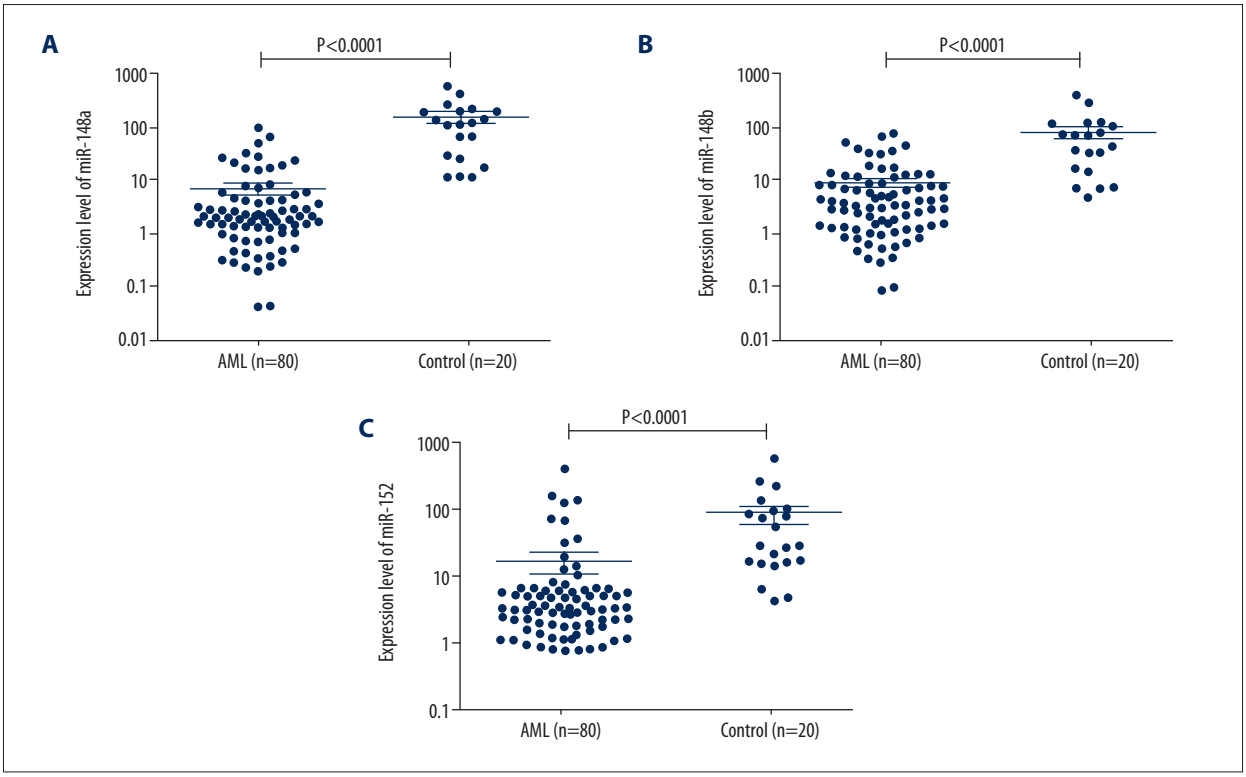

Figure 1. Expression of miR-148a/152 family in AML patients and healthy controls. (**A**) Expression of miR-148a. (**B**) Expression of miR-148b. (**C**) Expression of miR-152.

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Table 2. Relationships between expression of miR-148/152 and clinical/laboratory characteristics in AML.

	miR-148a			miR-148b			miR-152		
	High	Low	P	High	Low	P	High	Low	P
Female/Male	18/22	14/26	0.361	18/22	14/26	0.361	22/18	10/30	0.006
Age <60/≥60, n	28/12	29/11	0.805	34/6	23/19	0.003	32/8	25/15	0.084
Median WBC (range) ($\times 10^9$/L)	5.78 (1.41–221)	15.03 (1.12–193.27)	0.105	9.39 (1.54–92.97)	27.58 (1.12–221)	0.105	10.07 (1.54–92.97)	28.07 (1.12–221)	0.130
Median Hb (range) (g/L)	91 (55–143)	75 (46–139)	0.285	84.5 (55–125)	88.5 (46–108)	0.978	83.5 (55–125)	91.5 (46–143)	0.818
Median PLT (range) ($\times 10^9$/L)	41 (10–327)	25 (6–250)	0.035	38 (7–277)	32 (6–327)	0.379	38 (6–327)	32 (6–277)	0.387
Median blasts (range) (%)	75.2 (32.4–91.6)	77.2 (20.8–98)	1.000	77 (37.2–93.2)	77.5 (20.8–98%)	0.675	75 (29.6–93.2)	80.7 (20.8–98)	0.598
Low-risk, n (%)	16/21 (76.2%)	5/21 (23.8%)		18/21 (85.7%)	3/21 (14.3%)		7/21 (33.3%)	14/21 (66.7%)	
Intermediate-risk, n (%)	7/14 (50%)	7/14 (50%)	0.025	6/14 (42.9%)	8/14 (57.1%)	0.000	8/14 (57.1%)	6/14 (42.9%)	0.377
High-risk, n (%)	6/18 (33.3%)	12/18 (66.7%)		2/18 (11.1%)	16/18 (88.9%)		8/18 (44.4%)	10/18 (55.6%)	
Unknown, n (%)	11/27 (40.7%)	16/27 (59.3%)	–	14/27 (51.9%)	13/27 (48.1%)	–	17/27 (63.0%)	10/27 (37.0%)	–
Complete remission**, n (%)	25/33 (75.8%)	26/40 (65%)	0.319	27/33 (81.8%)	24/40 (60%)	0.043	21/33 (63.6%)	30/40 (75%)	0.292
Die during 1 year*** n (%)	6/25 (24%)	9/26 (34.6%)	0.406	7/27 (25.9%)	8/24 (33.3%)	0.562	7/21 (33.3%)	8/30 (26.7%)	0.607
Relapse during 1 year*** n (%)	11/25 (44%)	19/26 (73.1%)	0.035	12/27 (44.4%)	18/24 (75%)	0.027	14/21 (66.7%)	16/30 (53.3%)	0.341
Median miR expression (range)	2.16 (0.04–97)			3.815 (0.09–63.1)			3.24 (0.75–398.93)		

** Patients of M3 subtype were excluded; *** patients achieved CR were included.

Relationships between expression of miR-148/152 and clinical/laboratory characteristics in AML

The main clinical and laboratory features of the AML patients are shown in Table 2. The median expression level of miR-148a, miR-148b, and miR-152 (2.16, 3.815, and 3.24, respectively) were used as the cutoff point to divide the 80 AML patients into low and high expression groups. There was no significant difference in sex between patients with high and low expression of miR-148a/b. However, in patients with high expression of miR-152, there were more males than females (55% versus 25%, p=0.006). High expression of miR-148b showed a much younger age trend (85% versus 57.5%, p=0.003), but miR-148a and miR-152 did not. There was no significant difference in white blood cell count, hemoglobin, or percentage of blasts between the two groups. The platelet count was higher in patients with high expression of miR-148a than those with low expression (p=0.035).

Subsequently, we compared the expression of the miR-148/152 family according to the FAB subtypes. Patients were diagnosed as AML M1 (n=2), M2 (n=26), M3 (n=7), M4 (n=2), M5 (n=31), and M6 (n=12) in this study. The results showed that patients with M3 subtype had higher expression level of miR-148a and miR-148b than the other subtypes except for M1 (p<0.05). Expression of miR-152 was not significantly different among subtypes (Figure 2).

Furthermore, we compared the expression based on cytogenetic karyotypes in 62 AML patients and gene mutations types in 53 AML patients. According to the new classification of AML, patients in the present study included 11 AML patients with t(8;21)(q22;q22.1); six AML patients with inv(16)(p13.1q22); seven APL patients with PML-RARA; one AML patient with t(9;11)(p21.3;q23.3); two AML patients with t(6;9)(p23;q34.1); one AML patient with inv(3)(q21.3q26.2); 19 AML patients with complex karyotypes; and 15 AML patients with normal

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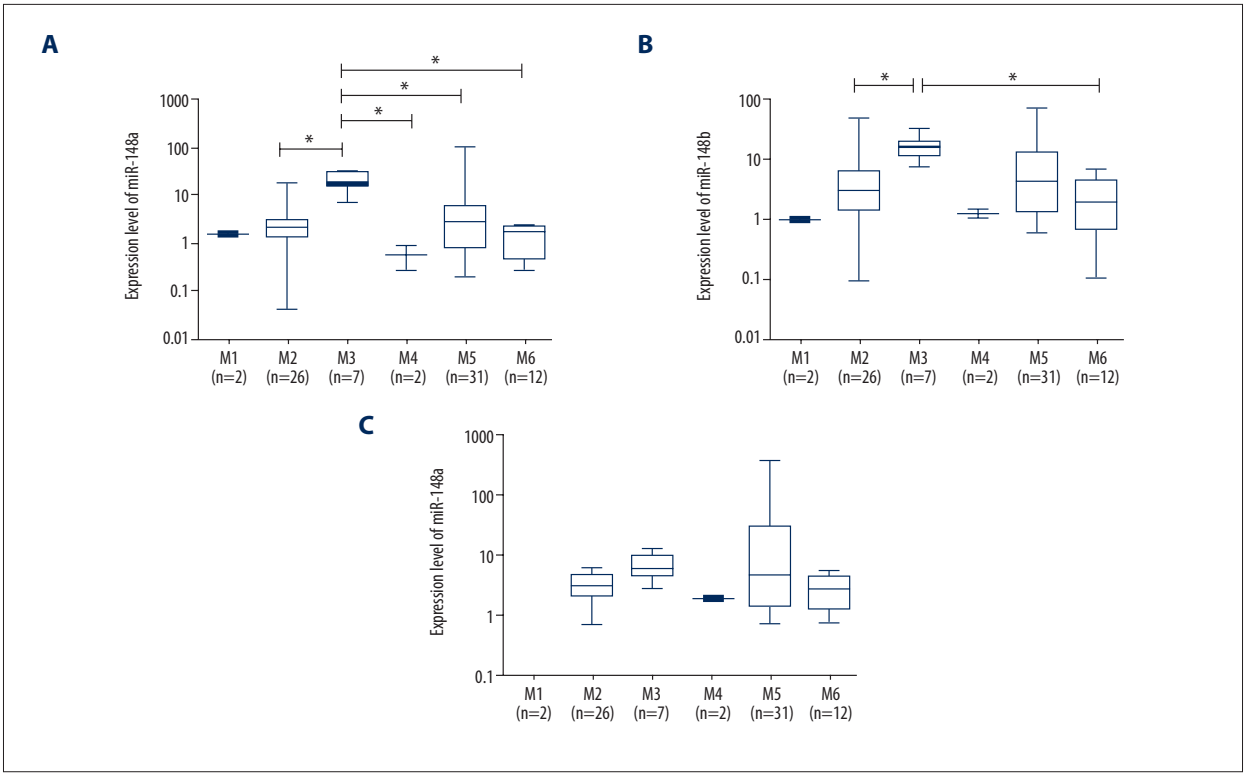

Figure 2. Expression of miR-148a/152 family in AML patients of different FAB subtypes. (**A**) Expression of miR-148a. (**B**) Expression of miR-148b. (**C**) Expression of miR-152. (* P<0.05).

karyotypes. Specifically, the results showed that expressions of miR-148a and miR-148b were much higher in AML patients with t(15;17) compared with patients with complex karyotype (p<0.05). Meanwhile, patients with t(15;17) showed a higher expression of miR-148a compared with patients with other kinds of abnormal cytogenetic karyotypes, and also showed a higher expression of miR-148b compared with patients with normal karyotype (p<0.05). With regard to patients with t(8;21), a higher expression of miR-148b was found compared with patients with complex karyotype (p<0.05, Figure 3).

We also found significantly higher expression of each miR-148/152 family members in the AML patients with NPM1 mutation than that of patients with FLT3-ITD/TKD mutations (p<0.05). Patients with NPM1 mutation showed higher expression levels of miR-148a and miR-148b compared with patients without mutation or DNMT3A mutation, respectively (p<0.05). Higher expressions of miR-148a and miR-148b were detected in patients with C-KIT mutation compared with patients with FLT3-ITD/TKD mutations (p<0.05). The level of miR-148a in patients with FLT3-ITD/TKD was significantly lower than that of patients with CEBPA mutation, and the level of miR-148b was significantly lower than that of the patients without mutations (p<0.05, Figure 4).

Meanwhile, we characterized the study group into low-risk, intermediate-risk, and high-risk groups according to the karyotypes distinction of AML combined with gene mutation types. The expression level of miR-148a and miR-148b were significantly different among the three groups (p=0.025, p=0.000, respectively, (Table 2).

Association of miR-148/152 expression with outcome of AML patients

Acute promyelocytic leukemia (APL) is a well-characterized subtype of AML (subtype M3). Molecular-targeting agents of all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) are essential drugs used in the treatment of APL, leading to a greatly improved prognosis. In the evaluation of therapeutic effects (CR rate, one year mortality rate, one year recurrence rate) in this study, we excluded the M3 subtype because the prognosis was significantly better than the other subtypes of AML.

There was no significant difference in CR between the higher and lower expression group of miR-148 and miR-152. Patients with higher expression of miR-148b showed a higher CR rate (p=0.043, Table 2). In the group who obtained CR, we evaluated the one year rate of death and relapse between higher and lower expression groups of the miR-148/152 family. The results showed there was no clear difference in the rate

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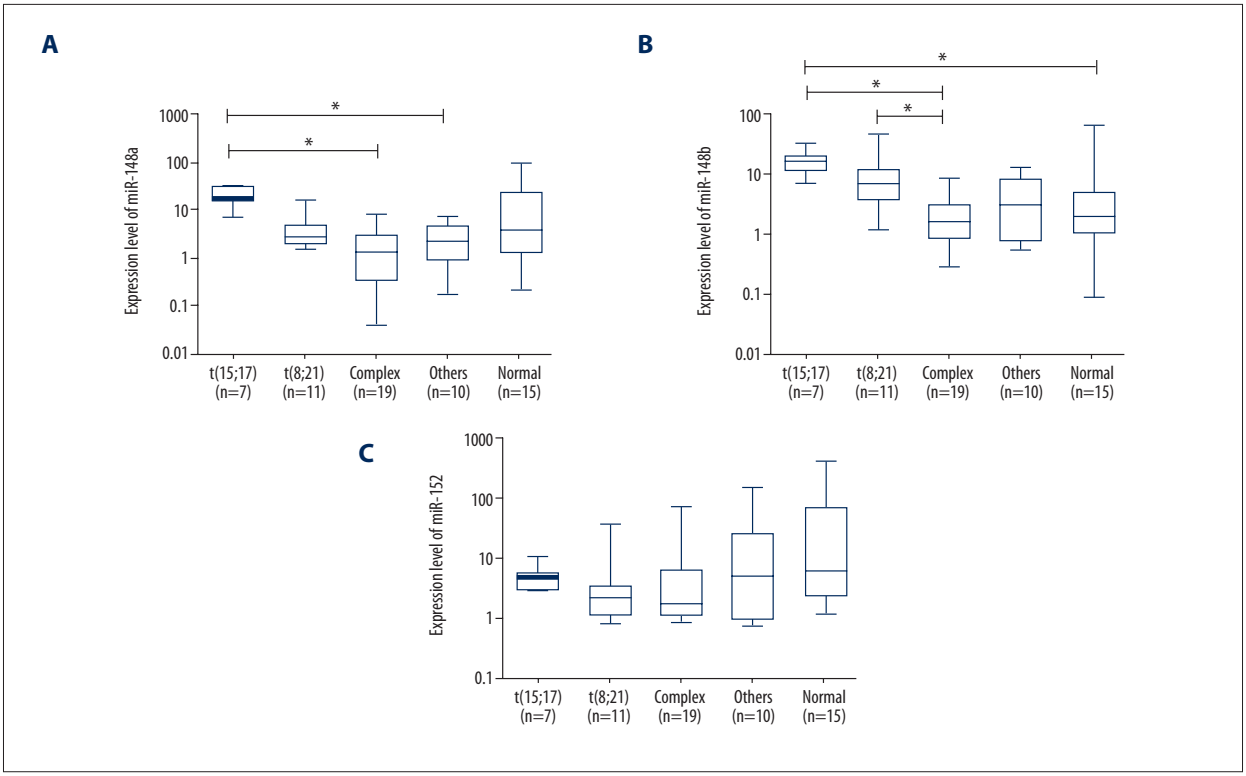

Figure 3. Expression of miR-148a/152 family in the AML patients with specific cytogenetic karyotypes. (**A**) Expression of miR-148a. (**B**) Expression of miR-148b. (**C**) Expression of miR-152. (* P<0.05).

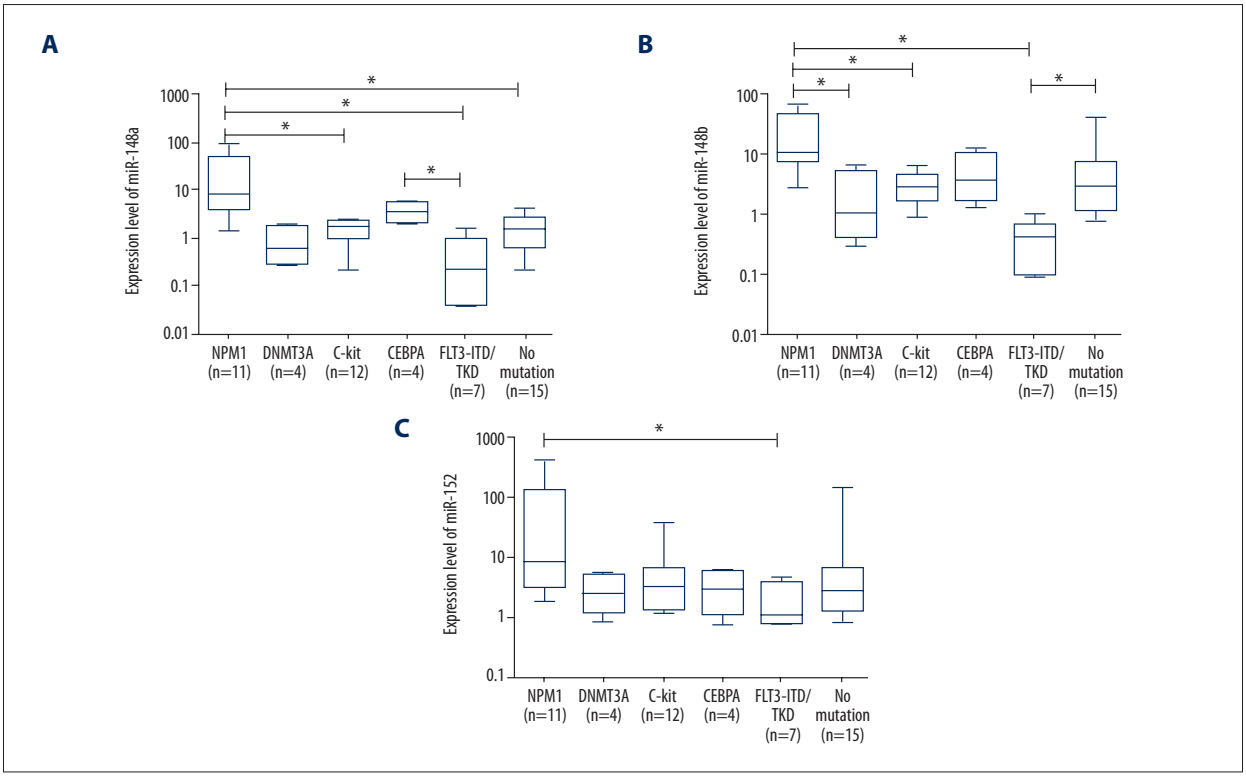

Figure 4. Expression of miR-148a/152 family in the AML patients with specific gene mutations. (**A**) Expression of miR-148a. (**B**) Expression of miR-148b. (**C**) Expression of miR-152. (* P<0.05).

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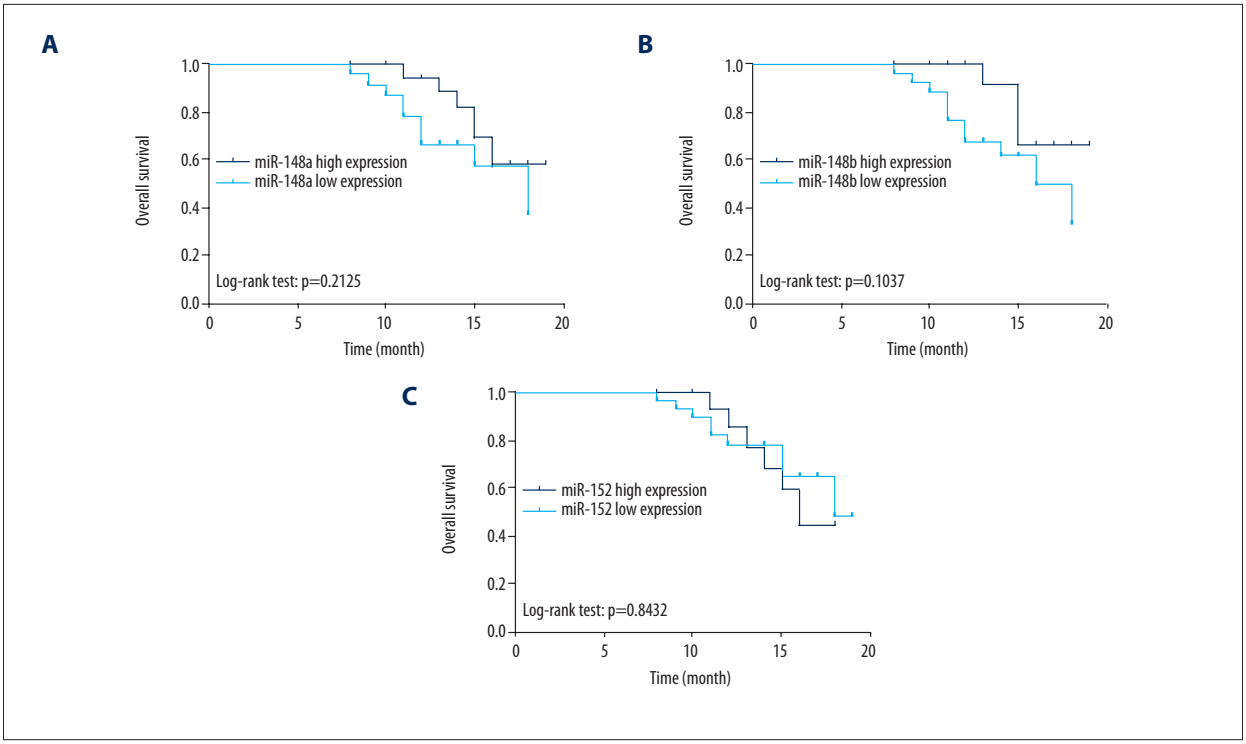

Figure 5. Kaplan-Meier survival curves for OS according to the high and low expression of miR-148/152 from 51 patients achieved CR. (**A**) Comparison between miR-148a high expression group and miR-148a low expression group. (**B**) Comparison between miR-148b high expression group and miR-148b low expression group. (**C**) Comparison between miR-152 high expression group and miR-152 low expression group.

of death between patients with higher and lower expression of miR-148a, miR-148b, and miR-152 (p=0.406; p=0.562; and p=0.607, respectively). However, relapse rates varied significantly between patients with higher and lower expression of miR-148a/b (p=0.035 and p=0.027, respectively). No significant difference in relapse rate was observed in patients with higher or lower expression of miR-152 (p=0.341, Table 2).

To investigate the prognostic impact of miR-148/152 expression in AML, survival analysis was performed among the 51 cases who obtained CR and had follow-up data, excluding M3 subtype. The patients with higher and lower miR-148/152 expression had similar OS (p=0.2125, p=0.1037, p=0.8432, respectively) (Figure 5A–5C). Remarkably, the cases with miR-148a/b high expression had greater difference in RFS than those with miR-148a/b low expression (p=0.0321, p=0.0159, respectively) (Figure 6A, 6B). As for miR-152, there was no significant difference in RFS between patients with higher and lower expression (p=0.6239, Figure 6C).

Subsequently, we also analyzed the OS and RFS on the basis of different risk stratification: low-risk, intermediate-risk, and high-risk groups according to the karyotypes distinction of AML combined with gene mutation types. There were significant difference in OS and RFS among the low-risk, intermediate-risk, and high-risk groups of AML (p=0.0051, p=0.003, respectively; Figure 7A, 7B). Further, in the high-risk group, patients with high expression of miR-148a showed significantly longer RFS than patients with low expression of miR-148a (p=0.0499; Figure 7C); while, in the intermediate-risk group, patients with high expression of miR-148b showed a distinct advantage (p=0.0114; Figure 7D). However, none of the subgroups showed a significant OS effect (p>0.05; data not shown).

Lastly, we analyzed the correlation between the expression levels among miR-148a, miR-148b, and miR-152. A strong positive correlation between expression of miR-148a and miR-148b was observed, with a correlation coefficient of 0.866 (p<0.05). A significant correlation was also observed between miR-148a and miR-152 (p<0.05, r=0.595), as well as between miR-148b and miR-152 (p<0.05, r=0.618; Figure 8A–8C).

Discussion

More and more studies have demonstrated that aberrant expression of miRs is closely related to the pathogenesis of almost all types of human cancers affecting the process of cell proliferation, apoptosis, angiogenesis, and differentiation [17]. To date, the upregulation or downregulation of specific miRs

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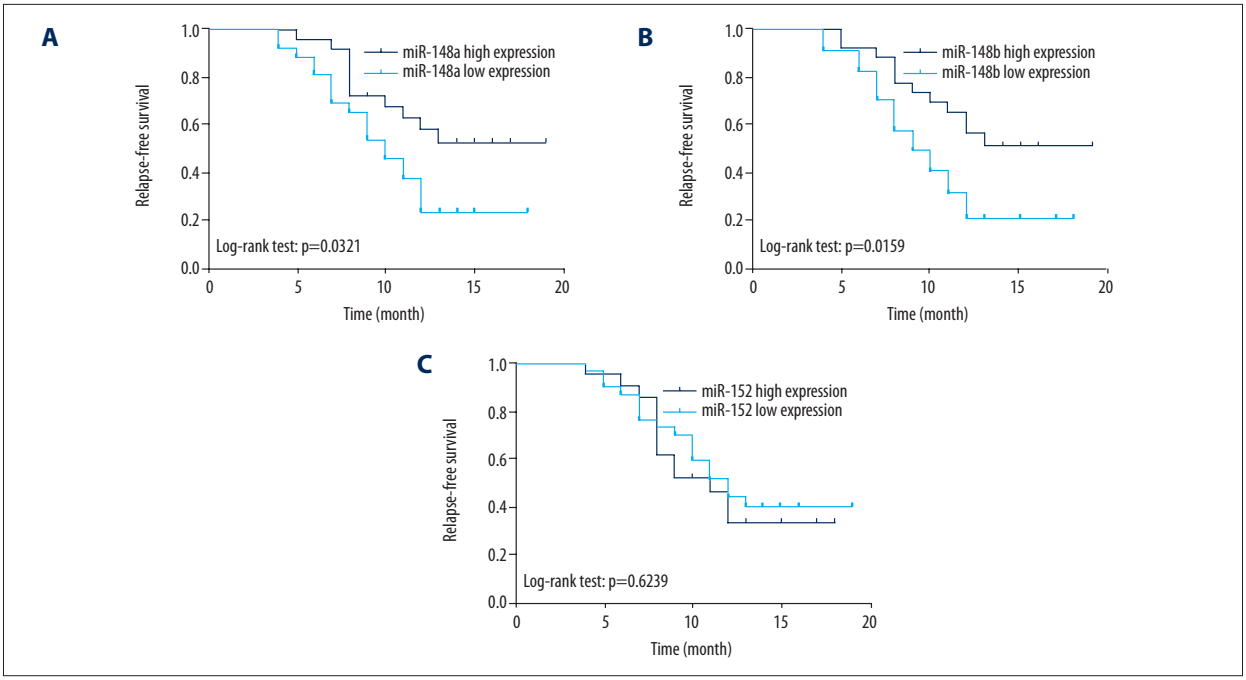

Figure 6. Kaplan-Meier survival curves for RFS according to the high and low expression of miR-148/152 from 51 patients achieved CR. (**A**) Comparison between miR-148a high expression group and miR-148a low expression group. (**B**) Comparison between miR-148b high expression group and miR-148b low expression group. (**C**) Comparison between miR-152 high expression group and miR-152 low expression group.

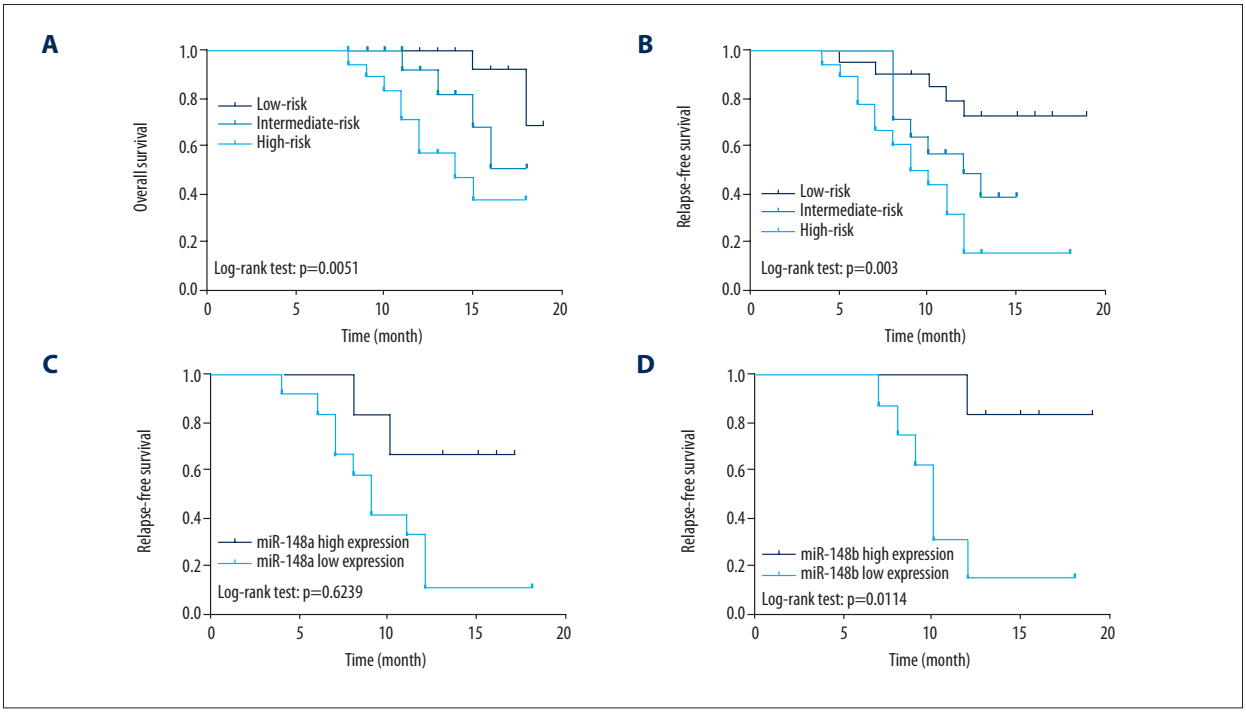

Figure 7. Kaplan-Meier survival curves for OS and RFS according to the different risk stratification. (**A**) OS among patients with low-risk, intermediate-risk and high-risk. (**B**) RFS among patients with low-risk, intermediate-risk and high-risk. (**C**) In the high-risk group, patients with high expression of miR-148a showed significantly longer RFS than patients with lower expression of miR-148a. (P=0.0499). (**D**) In the intermediate-risk group, patients with high expression of miR-148b showed significantly longer RFS than patients with lower expression of miR-148b. (P=0.0114).

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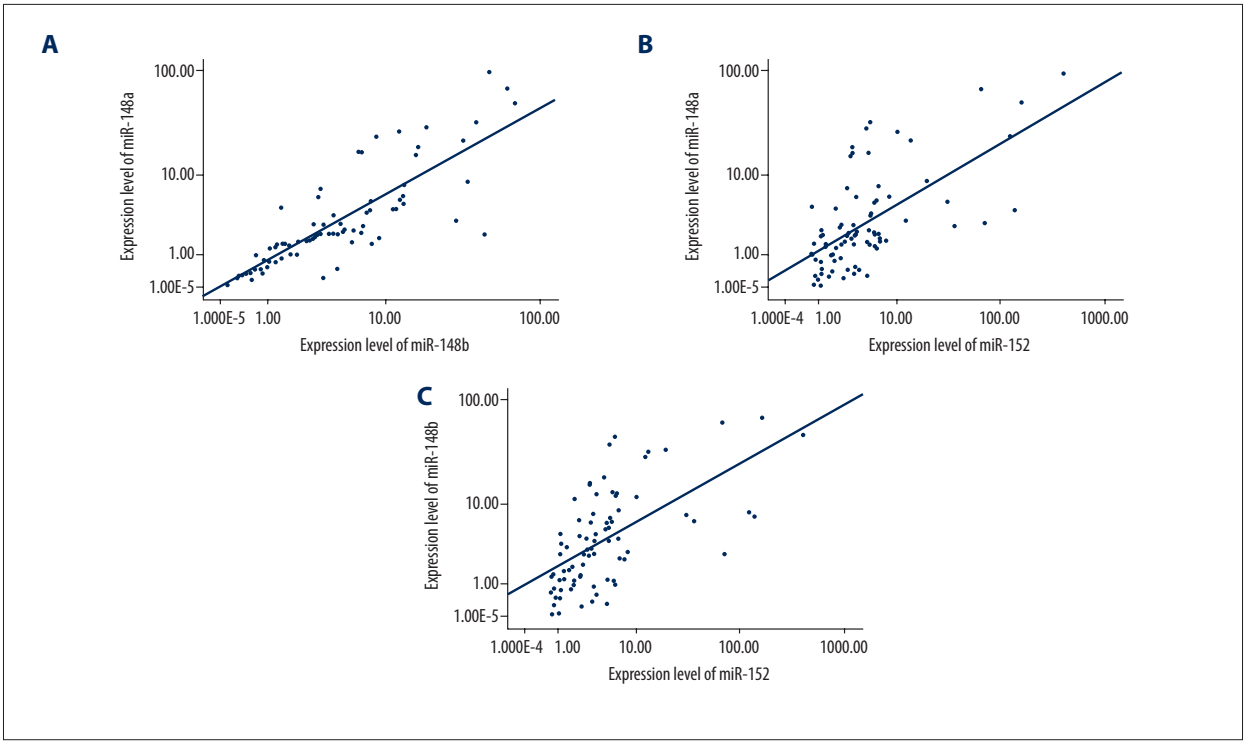

Figure 8. The correlation analysis between expression levels among miR-148a, miR-148b and miR-152. (**A**) Correlation analysis between expression level of miR-148a and miR-148b (P<0.05, r=0.866). (**B**) Correlation analysis between expression level of miR-148a and miR-152(P<0.05, r=0.595). (**C**) Correlation analysis between expression level of miR-148b and miR-152 (P<0.05, r=0.618).

detected at diagnosis have been correlated with chromosomal abnormalities and recurrent molecular aberrations, which have been associated with the risk stratification and outcomes of patients with AML [18–20].

Members of the miR-148/152 family have been found to have different expressions in diverse tumor tissues and play distinct biological functions [21–25]. However, little research on this subject has been published in the field of AML. A genome-wide microRNA profile study conducted by Niederwieser et al. [26] observed that high DNMT3B expression, which was an independent factor of adverse outcomes in older CN-AML patients, was associated with miR-148a down regulation. Fu et al. [27] showed that mitogen-activated protein kinase binding protein 1 (MAPKBP1) is an unfavorable prognostic biomarker in CN-AML, and miR-148a was downregulated in MAPKBP1-high patients with CN-AML. Schwind et al. [28] showed lower BAALC (brain and acute leukemia, cytoplasmic) and ERG (ETS-related gene) expression was associated with better outcomes in older (≥60 years) patients with CN-AML who presented with upregulation of miR-148a.

In the present study, we found abnormally decreased expression of all three miR-148/152 members in AML patients compared to healthy controls. Some differences were observed in patient characteristics between the high and low expression groups of the miR-148/152 family, including sex, age, and platelet count. According to the disease classification, karyotype, and gene mutation type of patients, the expression of miR-148/152 was significantly different. Patients with M3 subtype had higher expression of miR-148a and miR-148b than the other subtypes, which might indicate potential as good prognostic factors. In line with the risk stratification of AML [2], abnormal cytogenetics, like t(15;17) and t(8;21), as well as NPM1/CEBPA mutations, indicated a low risk. Normal cytogenetics and C-KIT mutations indicated intermediate risk, while complex cytogenetic and FLT3-ITD mutation indicated a high risk. In the present study, 53 patients had complete clinical data and could be risk-stratified. Our results showed high expression of miR-148a/b in patients with t(15;17). However, miR-148/152 expression of patients with t(8;21) varied greatly. The expression of miR-148a/b was lower in patients with complex cytogenetics. With the continuous development of sequencing technology, a variety of mutation types and AML prognosis are being identified as closely related [29–31]. Analysis of the mutation status of AML patients showed the expression of miR-148/152 was obviously elevated in patients with NPM1 mutation, which is consistent with a previous study conducted by Cammarata et al. [32] that observed an increased miR-148a expression in AML patients with NPM1 mutation or CN/CBF (core-binding factor)-AML.

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Nevertheless, in the present study, there was no significant difference between the higher and lower expression group of the miR-148/152 family in CR or OS. Only patients with high expression levels of miR-148b showed an advantage, which might have been related to age. However, higher levels of miR-148a/b still showed a greater benefit in relapse rate and RFS. In these patients we further analyzed OS and RFS based on risk stratification. As expected, there were significant differences in OS and RFS among the low-risk, intermediate-risk, and high-risk stratified groups of AML patients. Furthermore, in this subgroup comparison, none of the subgroups had a significant effect on OS. However, patients with high expression of miR-148a showed significantly longer RFS than patients with lower expression of miR-148a in the high-risk group. As for miR-148b, only two patients with high expression of miR-148b were classified as high-risk, hence it was not possible to analyze RFS. Even so, in the intermediate-risk group, patients with high expression of miR-148b showed a distinct advantage. In summary, the expression levels of miR-148a/b were correlated with genetic alteration characteristics and were generally consistent with the prognostic significance for individual risk groups.

With the deepening of the research on the miR-148/152 family, the research on the target genes in tumor-related diseases continues to emerge. It has been reported that the miR-148/152 family can target multiple genes (ROCK-1, DNMT1, Bcl-2, WNT10B, etc.) [33,34], and play vital biological functions in tumor cell proliferation, apoptosis, angiogenesis, etc. Some of these genes are important in AML as well. For example, DNMT1, one of the target genes of the miR-148/152 family, as predicted by bioinformatics, plays an important role in the pathogenesis of AML. One limitation of this study was that for some of the cases some clinical factors were not available to complete the risk stratification, and some subgroup cases were less likely to have an impact on the results. In the future, we should expand the sample size, and standardize the diagnosis and treatment requirements to further carry out functional experiments, targeting the function of target genes, and strive to further elucidate the pathogenesis of AML.

Conclusions

In general, our study suggested that miR-148/152 was downregulated in AML patients. Expression of miR-148/152 was closely associated with distinct clinical characteristics, as well as cytogenetic and gene mutation status in AML patients. Furthermore, higher expression levels of miR-148a/b showed a great benefit in relapse rate and RFS, especially in the subgroups of patients with high/intermediate-risk, which suggests the tumor-suppressor activities of miR-148a/b in AML. However, the precise molecular mechanisms of altered expression of the miR-148/152 family and their target genes need to be further investigated.

Conflict of interest

None.

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