Original Article

High expression of miR-107 and miR-17 predicts poor prognosis and guides treatment selection in acute myeloid leukemia

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Background: The prognostic significance of miR-107 and miR-17 in patients with acute myeloid leukemia (AML) remains unclear.

Methods: A total of 173 patients with *de novo* AML from the Cancer Genome Atlas database were enrolled in this study and further divided into a chemotherapy group (98 cases) and an allogeneic hematopoietic stem cell transplantation (allo-HSCT) group (75 cases) according to their therapy regimen.

Results: In the chemotherapy cohort, high miR-107 or miR-17 expression was associated with poorer overall survival (OS) and event-free survival (EFS). On the other hand, there were no significant differences in OS and EFS between the high- and low-expression subgroups in the allo-HSCT group. Next, we stratified the total number of patients with AML into high- and low-expression groups according to the median expression levels of miR-107 or miR-17. In the high miR-107 or miR-17 expression group, patients treated with allo-HSCT had longer OS than those treated with chemotherapy. In the low miR-107 or miR-17 expression group, no significant differences in OS and EFS were observed between the two therapy subgroups. When patients were further clustered into three groups (both low miR-107 and low miR-17, either high miR-107 or high miR-17, and both high miR-107 and high miR-17), patients with both high miR-107 and high miR-17 expression had the worst OS and EFS of the entire group and of the chemotherapy group. On the other hand, there were no significant differences in OS and EFS among the three subgroups in the allo-HSCT group. Cox regression confirmed the concurrence of high expression of miR-107 and miR-17 might act as an independent prognostic factor for EFS and OS in the entire group and the chemotherapy group. Bioinformatics analysis showed differentially expressed genes (DEGs) associated with miR-107 and miR-17 expression were mainly enriched in multiple metabolic processes.

Conclusions: The combination of miR-107 and miR-17 provides prognostic significance for patients with AML and should be considered in the clinical selection of the optimal treatment regimen when deciding between chemotherapy and allo-HSCT.

Keywords: miR-107; miR-17; acute myeloid leukemia (AML); prognosis; therapy

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Introduction

Acute myeloid leukemia (AML) is an aggressive malignancy characterized by uncontrolled proliferation, blocked differentiation, and reduced apoptosis of hematopoietic stem cells (1). Despite advances in the treatment of AML during past decades, the clinical prognosis remains unsatisfactory and varies with factors such as age, karyotype, cytogenetic characteristics, and treatment selection (2). Therefore, the identification of novel prognostic markers is needed to improve risk stratification and optimize the selection of treatment options for patients with AML.

MicroRNAs (miRNAs) are regarded as small noncoding RNAs of 20–24 nucleotides that negatively modulate gene expression by directly binding to the 3'-untranslated region (UTR) of target mRNA (3). MiRNAs play vital roles in many physiologic processes, including cell proliferation, differentiation, apoptosis, and self-renewal (4). Aberrant miRNAs are widely involved in cancer biologies, such as tumorigenesis, tumor growth, invasion, metastasis, and angiogenesis (5), and recently, several cancer-associated miRNAs were reported to function as biomarkers to predict the prognosis and treatment response of patients with AML (6-8). For instance, low expression of miR-340 contributed to a lower complete remission rate of patients with AML (9), and in patients who received chemotherapy, upregulated miR-338 was associated with shorter event-free survival (EFS) and overall survival (OS) (10). Patients with AML with high expression levels of miR-212 were also found to have a prolonged OS and EFS (11). In addition, upregulated miR-181a expression correlated with better survival in patients with cytogenetically normal AML (CN-AML) (12), while miR-3151 expression negatively correlated with survival in CN-AML (13).

Here, for the first time, we evaluate the prognostic value of miR-107 and miR-17 for patients with AML according to the therapy regimen. A total of 173 patients with *de novo* AML from the Cancer Genome Atlas (TCGA) database were enrolled in this study and further divided into a chemotherapy group and an allogeneic hematopoietic stem cell transplantation (allo-HSCT) group. The prognostic roles of miR-107 and miR-17, as well as the combination of the two miRNAs, were analyzed. Our results suggested both miR-107 and miR-17 were independent prognosticators of poor survival in patients with AML, whose adverse prognosis could be overcome by allo-HSCT. More importantly, the concurrence of high expression levels of miR-107 and miR-17 correlated with worse survival, which should be considered in the clinical selection of the optimal treatment regimen when deciding between chemotherapy and allo-HSCT. We present the following article in accordance with the REMARK reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2484/rc).

Highlight box

Key findings

- Both miR-107 and miR-17 were independent prognosticators of poor survival in patients with acute myeloid leukemia (AML), whose adverse prognosis could be overcome by allogeneic hematopoietic stem cell transplantation (allo-HSCT). The combined criteria of miR-107 and miR-17 should be regarded as an unfavorable prognosticator for AML patients, which might improve its risk stratification and improve patient outcomes by selecting patients for allo-HSCT.

What is known and what is new?

- The role of miR-107 and miR-17 remains controversial for different cancer types.
- High expression of miR-107, as well as miR-17, predicted an unfavorable outcome for patients with AML who received chemotherapy but not allo-HSCT.

What is the implication, and what should change now?

- The combined criteria of miR-107 and miR-17 provides prognostic significance for patients with AML and should be considered in the clinical selection of the optimal treatment regimen when deciding between chemotherapy and allo-HSCT. Further studies are needed to reveal the detailed mechanism of miR-107 and miR-17 in AML.

Methods

Patients

A total of 173 patients with *de novo* AML were enrolled in this study. According to the therapy regimen, patients were further divided into a chemotherapy group (98 cases) and an allo-HSCT group (75 cases). The expression data of miR-107 and miR-17, the treatment regimen, the clinical outcomes, and the characteristics at diagnosis, including sex, age, peripheral white blood cell (WBC) count, blast percentages in bone marrow (BM), French-American-British (FAB) subtype, cytogenetic risk, and gene mutations, were obtained from TCGA website. For microRNA-seq data, read counts for each sample were normalized to reads per million. OS was defined as the time from diagnosis to death or the last follow-up, and EFS was defined as the time interval from diagnosis to the date of induction failure, relapse, or death due to any cause. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Statistical analysis

SPSS 25.0 (IBM Corp., Armonk, NY, USA) was applied for statistical analyses. For categorical variables and continuous variables, Pearson chi-square analysis, Fisher's exact test, and the Mann–Whitney *U* test were performed to compare the differences between the two groups. Kaplan–Meier and Cox regression (univariate and multivariate) models were conducted to determine the effect of miR-107/miR-17 expression on EFS and OS. All tests were two-sided, and a P value <0.05 was considered statistically significant.

Results

Correlation of miR-107 or miR-17 level with clinical features in AML

To analyze the clinical relevance of miR-107 or miR-17 expression in AML, the whole cohort of patients was divided into a chemotherapy group and an allo-HSCT group. Each group was then further divided into high-expression and low-expression subgroups based on the median level of miR-107 or miR-17. The association between the clinical characteristics and the expression of miR-107 or miR-17 in the different treatment groups is listed in *Tables 1*,*2*. In the chemotherapy group, the percentages of males (P=0.009) and intermediate karyotype (P=0.036) in the miR-107^{high} subgroup were higher than the miR-107^{low} subgroup. In the miR-17^{high} subgroup, patients had more intermediate karyotype (P=0.036), more complex karyotype (P=0.045), more unfavorable risk (P=0.016), and less favorable risk cases (P=0.042). There were no striking differences in age, WBC, BM blasts, FAB classification, and mutation frequencies of well-known prognostic genes (*NPM1*, *IDH1*, *IDH2*, *MLL-PTD*, *NRAS*, *KRAS*, and *TP53*) between the low and high miR-107/17 expression groups. In the allo-HSCT group, patients with high miR-107 expression had less *NPM1* mutation (P=0.025), less normal karyotype (P=0.048), and more intermediate karyotype (P=0.030), while there were no significant differences in clinical features between the miR-17^{high} and the miR-17^{low} subgroups.

Prognostic value of miR-107 and miR-17 in patients who received chemotherapy or allo-HSCT

To evaluate the prognostic significance of miR-107 and miR-17 in patients who received chemotherapy or allo-HSCT, the Kaplan–Meier method and log-rank test were performed. In the chemotherapy cohort, high miR-107 expression was significantly correlated with shorter OS (P=0.008; *Figure 1A*) and EFS (P=0.010; *Figure 1B*). Similarly, patients with high miR-17 expression had worse OS (P=0.049; *Figure 1C*) and EFS (P=0.032; *Figure 1D*). However, in the allo-HSCT cohort, no differences were observed in OS and EFS between the high and low miR-107/miR-17 expression subgroups (all P values >0.05; *Figure 1E-1H*). These results indicated high expression levels of miR-107, as well as miR-17, predicted an unfavorable outcome for patients with AML who received chemotherapy but did not receive allo-HSCT.

Allo-HSCT overcomes the poor prognosis of the high expression of miR-107 or miR-17 in AML

Considering no prognostic value of miR-107 or miR-17 was found in patients who received allo-HSCT, we further analyzed whether it could overcome the poor prognosis of high miR-17/miR-107 expression compared with chemotherapy. First, the whole cohort was stratified into two groups according to the median expression levels of miR-107 or miR-17. Each group was further distributed into the chemotherapy and the allo-HSCT subgroups. In the miR-107^{high} group, patients treated with allo-HSCT had similar EFS (P=0.208) but longer OS (P=0.009) compared with those treated with chemotherapy (*Figure 2A*,*2B*), while in the miR-107^{low} group, no significant differences were observed in OS or EFS between the chemotherapy and allo-HSCT subgroups (*Figure 2C*,*2D*). Similar results were obtained in the miR-17^{high} and the miR-17^{low} groups (*Figure 2E-2H*). Therefore, allo-HSCT might be an effective therapy in patients with AML with high expression levels of miR-107 or miR-17.

Combination of miR-107 and miR-17 forecast a more accurate prognosis

We next evaluated the correlation between miR-107 and miR-17 expression levels. As shown in *Figure 3*, patients with relatively higher miR-107 expression tended to present higher expression of miR-17, and Spearman rank correlation analysis confirmed a positive correlation between the two (Spearman r=0.315; P<0.001). To explore the prognostic significance of the combination of miR-107 and miR-17 in the different cohorts, patients were further clustered into three groups (both miR-107^{low} and miR-17^{low}, either miR-107^{high} or miR-17^{high}, and both miR-107^{high} and miR-17^{high}). In the entire group and the chemotherapy group, there

Table 1 Correlations between miR-107 expression and clinical features in patients with AML

Patient features	Chemotherapy group			Allo-HSCT group		
	High miR-107 (n=49)	Low miR-107 (n=49)	P value	High miR-107 (n=37)	Low miR-107 (n=38)	P value
Sex, male/female	32/17	19/30	0.009	24/13	18/20	0.127
Age, median [range], years	64 [22–82]	61 [29–88]	0.154	50 [18–65]	52 [21–72]	0.518
WBC, median [range], $\times 10^9$/L	12.1 [0.7–298.4]	14.3 [0.4–297.4]	0.629	15.8 [0.8–223.8]	30.1 [0.6–118.8]	0.266
BM blasts/%, median [range]	73.0 [30–98]	74.0 [32–100]	0.782	63.0 [30–99]	79.5 [35–100]	0.107
FAB subtypes/n (%)						
M0	3 (6.1)	4 (8.2)	1.000	5 (13.5)	4 (10.5)	0.966
M1	11 (22.4)	9 (18.4)	0.616	9 (24.3)	14 (36.8)	0.240
M2	9 (18.4)	10 (20.4)	0.798	11 (29.7)	8 (21.1)	0.388
M3	5 (10.2)	10 (20.4)	0.161	0 (0)	2 (5.3)	0.493
M4	13 (26.5)	10 (20.4)	0.475	7 (18.9)	7 (18.4)	0.956
M5	6 (12.2)	6 (12.2)	1.000	3 (8.1)	2 (5.3)	0.975
M6	1 (2.0)	0 (0)	1.000	1 (2.7)	0 (0)	0.493
M7	1 (2.0)	0 (0)	1.000	1 (2.7)	0 (0)	0.493
No data	0 (0)	0 (0)		0 (0)	1 (2.6)	1.000
Karyotype/n (%)						
Normal	18 (36.7)	25 (51.0)	0.154	13 (35.1)	22 (57.9)	0.048
Intermediate	8 (16.3)	1 (2.0)	0.036	8 (21.6)	1 (2.6)	0.030
Poor	2 (4.1)	3 (6.1)	1.000	2 (5.4)	3 (7.9)	1.000
Complex	5 (10.2)	5 (10.2)	1.000	6 (16.2)	6 (15.8)	0.960
MLL	3 (6.1)	0 (0)	0.241	2 (5.4)	1 (2.6)	0.981
CBFβ::MYH11	5 (10.2)	2 (4.1)	0.433	4 (10.8)	1 (2.6)	0.339
RUNX1::RUNX1T1	2 (4.1)	4 (8.2)	0.673	0 (0)	1 (2.6)	1.000
PML::RARA	5 (10.2)	9 (18.4)	0.248	0 (0)	2 (5.3)	0.493
BCR::ABL1	0 (0)	0 (0)		2 (5.4)	0 (0)	0.240
No data	1 (2.0)	0 (0)	1.000	0 (0)	1 (2.6)	1.000
Risk (cyto)/n (%)						
Favorable	12 (24.5)	15 (30.6)	0.498	4 (10.8)	4 (10.5)	1.000
Intermediate	27 (55.1)	26 (53.1)	0.839	21 (56.8)	23 (60.5)	0.740
Unfavorable	9 (18.4)	8 (16.3)	0.790	12 (32.4)	10 (26.3)	0.561
No data	1 (2.0)	0 (0)	1.000	0 (0)	1 (2.6)	1.000
Gene mutations						
NPM1 (+/–)	11/38	16/33	0.258	6/31	15/23	0.025
IDH1 (+/–)	2/47	5/44	0.433	4/33	7/31	0.352
IDH2 (+/–)	6/43	2/47	0.268	4/33	4/34	1.000
MLL-PTD (+/–)	3/46	2/47	1.000	2/35	2/36	1.000
NRAS (+/–)	4/45	4/45	1.000	4/33	1/37	0.339
KRAS (+/–)	3/46	2/47	1.000	0/37	2/36	0.493
TP53 (+/–)	6/43	3/46	0.484	2/35	2/36	1.000

Categorical and continuous variables are presented as counts (percentages) and median (interquartile range), respectively. AML, acute myeloid leukemia; WBC, white blood cell; BM, bone marrow; FAB, French-American-British; Allo-HSCT, allogeneic hematopoietic stem cell transplantation.

Table 2 Correlations between miR-17 expression and clinical features in patients with AML

Patient features	Chemotherapy group			Allo-HSCT group		
	High miR-17 (n=49)	Low miR-17 (n=49)	P value	High miR-17 (n=37)	Low miR-17 (n=38)	P value
Sex, male/female	29/20	22/27	0.157	22/15	20/18	0.551
Age, median [range], years	64 [22–81]	61 [25–88]	0.159	55 [18–72]	47 [21–65]	0.402
WBC, median [range], $\times10^9$/L	13.1 [1.5–298.4]	11.0 [0.4–297.4]	0.191	30.5 [0.8–223.8]	29.4 [0.6–118.8]	0.368
BM blats/%, median [range]	74 [32–98]	72 [30–100]	0.582	71 [30–99]	71.5 [34–100]	0.491
FAB subtypes/n (%)						
M0	5 (10.2)	2 (4.1)	0.433	4 (10.8)	5 (13.2)	1.000
M1	12 (24.5)	8 (16.3)	0.316	13 (35.1)	10 (26.3)	0.408
M2	11 (22.4)	8 (16.3)	0.443	7 (18.9)	12 (31.6)	0.208
M3	4 (8.2)	11 (22.4)	0.050	0 (0)	2 (5.3)	0.493
M4	9 (18.4)	14 (28.6)	0.233	6 (16.2)	8 (21.1)	0.591
M5	7 (14.3)	5 (10.2)	0.538	4 (10.8)	1 (2.6)	0.339
M6	1 (2.0)	0 (0)	1.000	1 (2.7)	0 (0)	0.493
M7	0 (0)	1 (2.0)	1.000	1 (2.7)	0 (0)	0.493
No data	0 (0)	0 (0)		1 (2.7)	0 (0)	0.493
Karyotype/n (%)						
Normal	18 (36.7)	25 (51.0)	0.154	18 (48.6)	17 (44.7)	0.734
Intermediate	8 (16.3)	1 (2.0)	0.036	5 (13.5)	4 (10.5)	0.966
Poor	4 (8.2)	1 (2.0)	0.359	3 (8.1)	2 (5.3)	0.975
Complex	8 (16.3)	2 (4.1)	0.045	5 (13.5)	7 (18.4)	0.562
MLL	1 (2.0)	2 (4.1)	1.000	2 (5.4)	1 (2.6)	0.981
CBFβ::MYH11	1 (2.0)	6 (12.2)	0.117	2 (5.4)	3 (7.9)	1.000
RUNX1::RUNX1T1	4 (8.2)	2 (4.1)	0.673	0 (0)	1 (2.6)	1.000
PML::RARA	4 (8.2)	10 (20.4)	0.083	0 (0)	2 (5.3)	0.493
BCR::ABL1	0 (0)	0 (0)		2 (5.4)	0 (0)	0.240
No data	1 (2.0)	0 (0)	1.000	0 (0)	1 (2.6)	1.000
Risk (cyto)/n (%)						
Favorable	9 (18.4)	18 (36.7)	0.042	2 (5.4)	6 (15.8)	0.279
Intermediate	26 (53.1)	27 (55.1)	0.839	23 (62.2)	21 (55.3)	0.544
Unfavorable	13 (26.5)	4 (8.2)	0.016	12 (32.4)	10 (26.3)	0.561
No data	1 (2.0)	0 (0)	1.000	0 (0)	1 (2.6)	1.000
Gene mutations						
NPM1 (+/–)	15/34	12/37	0.498	8/29	13/25	0.225
IDH1 (+/–)	3/46	4/45	1.000	4/33	7/31	0.352
IDH2 (+/–)	4/45	4/45	1.000	4/33	4/34	1.000
MLL-PTD (+/–)	3/46	2/47	1.000	2/35	2/36	1.000
NRAS (+/–)	4/45	4/45	1.000	1/36	4/34	0.371
KRAS (+/–)	4/45	1/48	0.359	1/36	1/37	1.000
TP53 (+/–)	6/43	3/46	0.484	2/35	2/36	1.000

Categorical and continuous variables are presented as counts (percentages) and median (interquartile range), respectively. AML, acute myeloid leukemia; WBC, white blood cell; BM, bone marrow; FAB, French-American-British; Allo-HSCT, allogeneic hematopoietic stem cell transplantation.

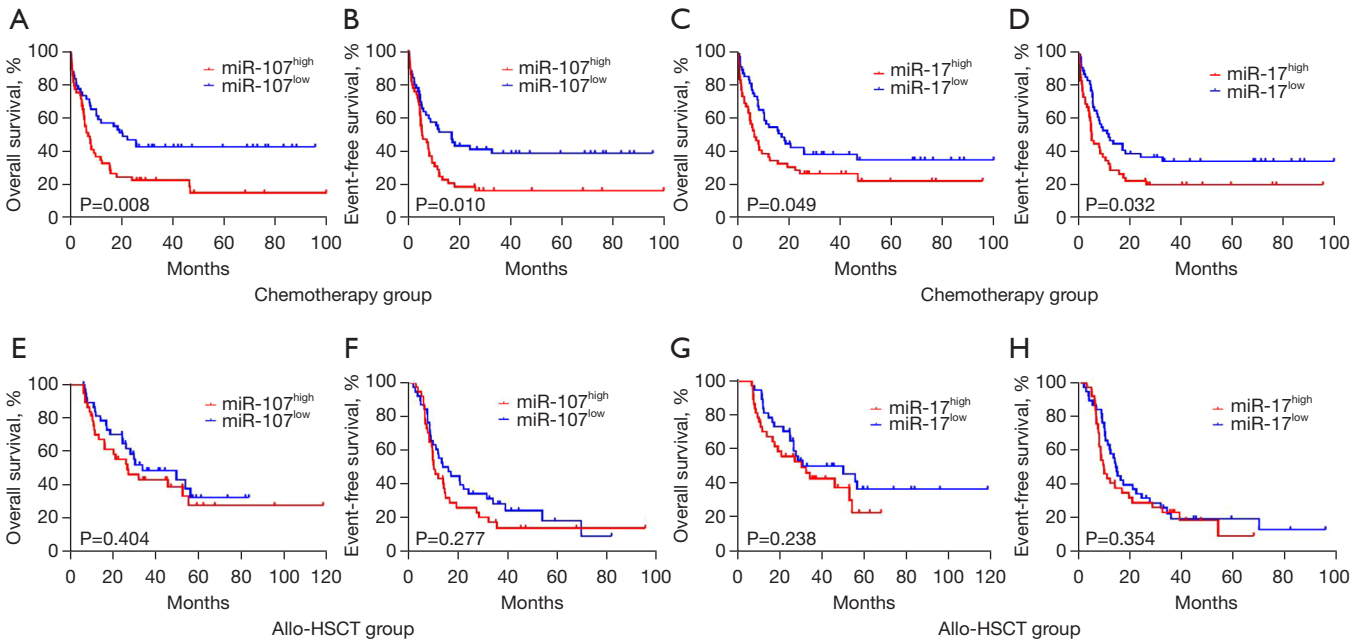

Figure 1 Prognostic value of miR-107 and miR-17 expression in the chemotherapy group and the allo-HSCT group. (A,B) In the chemotherapy group, patients with high miR-107 expression had shorter OS and EFS. (C,D) In the chemotherapy group, patients with high miR-17 expression had shorter OS and EFS. (E,F) In the allo-HSCT group, no significant difference was observed in OS and EFS between high and low miR-107 expressers. (G,H) In the allo-HSCT group, no significant differences were observed in OS and EFS between high and low miR-17 expressers. allo-HSCT, allogeneic hematopoietic stem cell transplantation; OS, overall survival; EFS, event-free survival.

were significant differences among the three subgroups for OS (P=0.009, P=0.015) and EFS (P=0.020, P=0.014; *Figure 4A-4D*). Moreover, we found that patients with both high miR-107 and high miR-17 expression had the worst OS and EFS in the entire group and the chemotherapy group. On the other hand, there were no significant differences in OS and EFS between the three groups in the allo-HSCT cohort (*Figure 4E,4F*). These results implied that the combined criteria of miR-107 and miR-17 could be a more accurate prognostic marker for patients with AML, whose adverse prognosis might be overcome by allo-HSCT.

Combination of miR-107 and miR-17 expression acted as an independent prognostic factor for EFS and OS in the chemotherapy cohort

We further performed univariate and multivariate cox regression analyses to validate the prognostic value of the combination of miR-107 and miR-17 expression in different groups. For the entire group, univariate cox regression indicated the high expression of both miR-107 and miR-17 was associated with poorer EFS [hazard ratio (HR) =1.816; 95% confidence interval (CI): 1.190–2.771; P=0.006] and OS (HR =2.048; 95% CI: 1.279–3.279; P=0.003), and mutation in TP53 was unfavorable for both EFS and OS (all P values <0.001). Multivariate analysis revealed high expression levels of both miR-107 and miR-17 remained independently predictive of reduced EFS (P=0.010) and OS (P=0.007) even in the presence of other covariates (*Table 3*).

For the chemotherapy group, univariate cox regression suggested patients with both high miR-107 and miR-17 had shorter EFS (HR =2.404; 95% CI: 1.317–4.388; P=0.004) and OS (HR =2.430; 95% CI: 1.313–4.498; P=0.005), and TP53 mutation had an adverse effect on EFS and OS (all P values <0.05). Multivariate analysis demonstrated high expression levels of both miR-107 and miR-17 were independently associated with adverse EFS and OS after adjusting for the *TP53* mutation status (P<0.05; *Table 4*).

For the allo-HSCT group, univariate analysis revealed patients with *MLL-PTD* mutation had shorter EFS (HR =6.032; 95% CI: 2.042–17.816; P=0.001) and *TP53* mutation was correlated with adverse OS (HR =4.217; 95% CI: 1.422–12.503; P=0.009). Multivariate analysis showed *MLL-PTD* mutation was an independent risk factor for

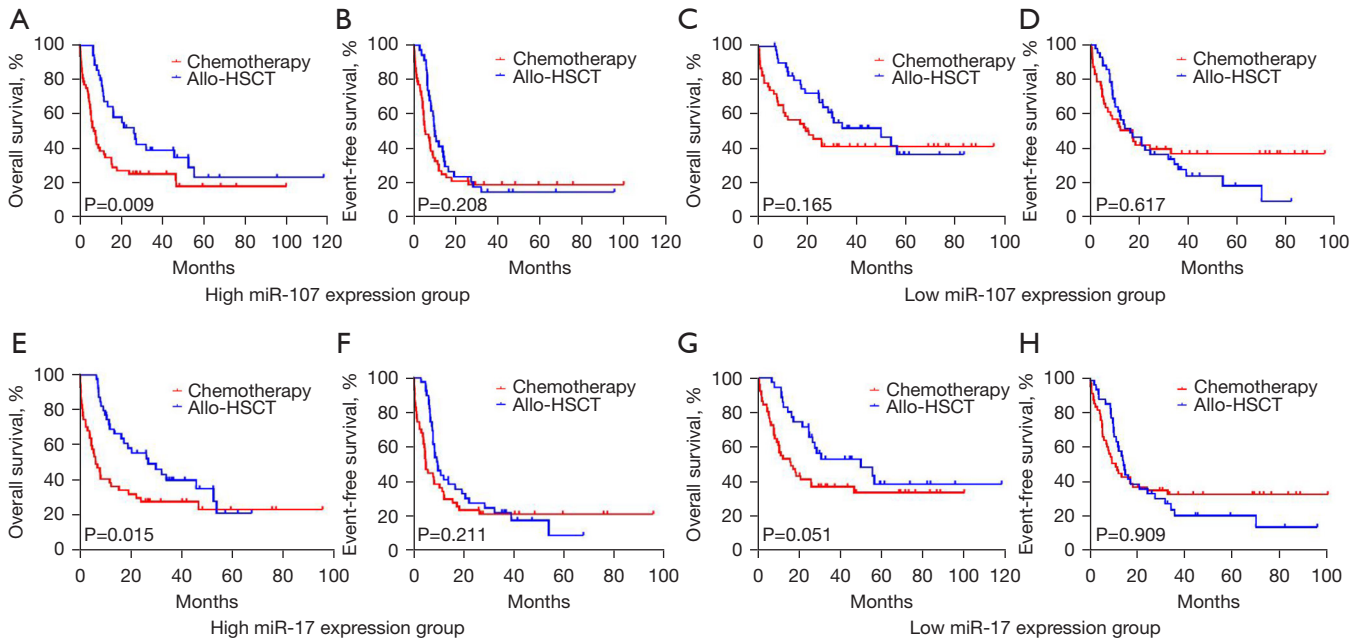

Figure 2 Kaplan–Meier survival curves in high and low miR-107/miR-17 expression groups. (A,B) In the high miR-107 expression group, patients treated with allo-HSCT had longer OS but similar EFS compared with those treated with chemotherapy. (C,D) In the low miR-107 expression group, no significant differences were observed in OS and EFS between the chemotherapy subgroup and the allo-HSCT subgroup. (E,F) In the high miR-17 expression group, patients treated with allo-HSCT had longer OS but similar EFS compared with those treated with chemotherapy. (G,H) In the low miR-17 expression group, no significant differences were observed in OS and EFS between the chemotherapy and the allo-HSCT subgroups. allo-HSCT, allogeneic hematopoietic stem cell transplantation; OS, overall survival; EFS, event-free survival.

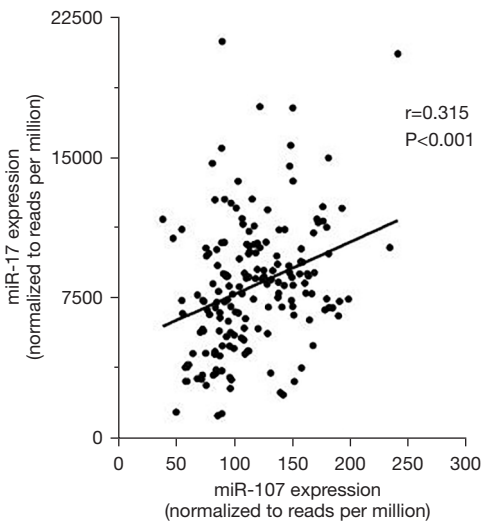

Figure 3 Correlation between miR-107 and miR-17 was analyzed. The P value is from the Spearman rank correlation.

EFS (P<0.001) and TP53 mutation was an independent risk factor for OS (P=0.007). However, high expression levels of both miR-107 and miR-17 had no independent effect on EFS and OS in either the univariate or the multivariate analysis (all P values >0.05; *Table 5*).

Screening of differentially expressed genes (DEGs)

To better understand the function of miR-107 and miR-17 in patients with AML, DEGs were screened between both low- and high-expression groups using RNA sequencing data set from TCGA database. A total of 203 DEGs were identified, including 183 upregulated and 20 downregulated genes (*Figure 5*). The target genes of miR-107 and miR-17 were predicted by the miRDB, miRWalk and TargetScan databases, and among the screened DEGs, *DNAJC9*, *HMGA1*, *IPO9*, *LRPPRC*, *MDN1*, *NECAP1*, *PHB*, *POLA2*, *PRMT5*, *RHOBTB2*, *TTF2*, *TTLL12*, *VCP*, and *ZHX3* were considered the possible target genes of miR-107. In addition, we identified *BRCA1*, *C21orf58*, *CHAF1A*,

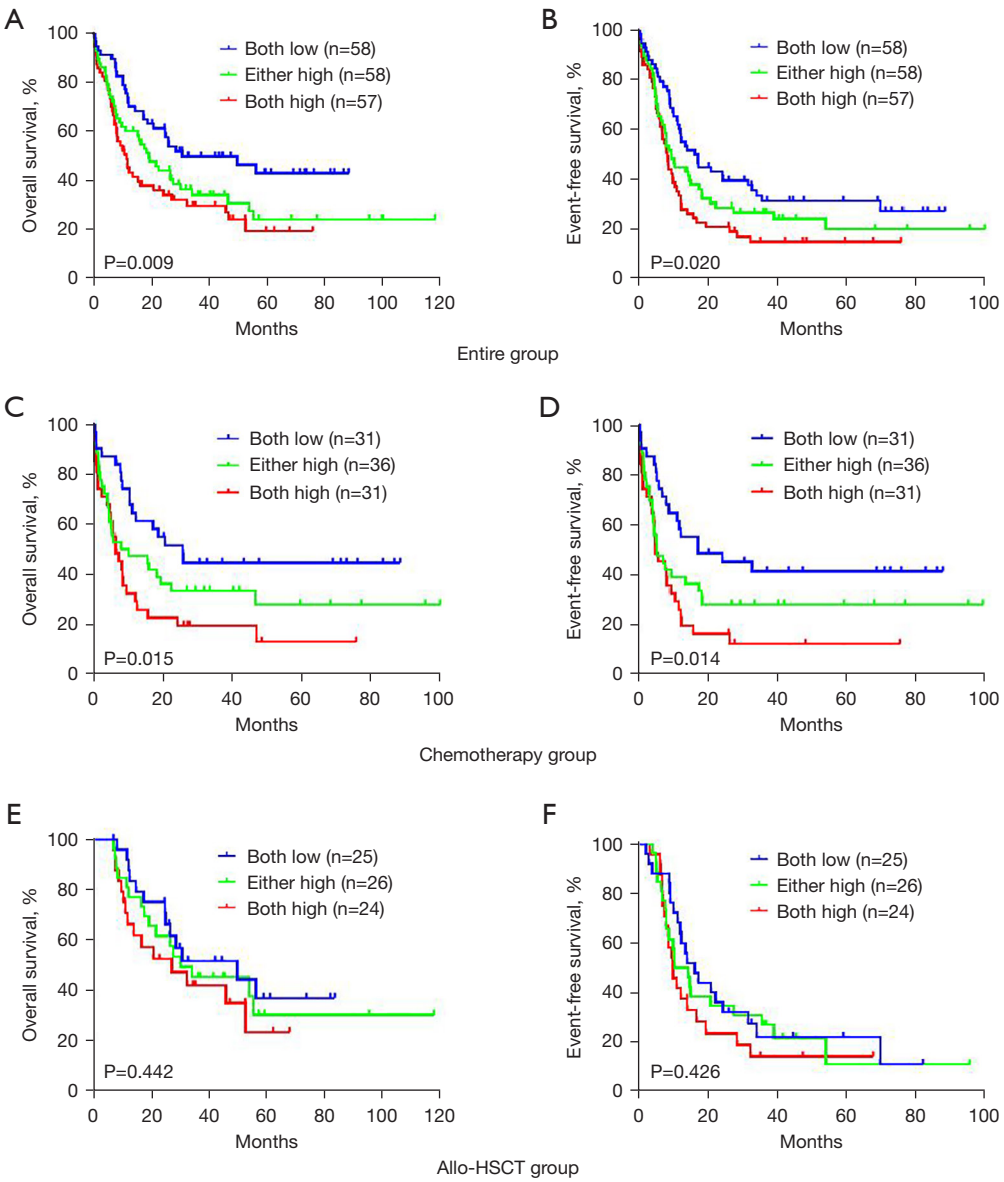

Figure 4 Kaplan–Meier survival curves based on the combination of miR-107 and miR-17 expression in AML. (A,B) Patients were clustered into three subgroups: both low miR-107 and low miR-17 expression, either high miR-107 or high miR-17 expression, and both high miR-107 and high miR-17 expression. In the entire group, patients with both high miR-107 and high miR-17 expression had the worst OS and EFS. (C,D) In the chemotherapy group, patients with both high miR-107 and high miR-17 expression had the worst OS and EFS. (E,F) In the allo-HSCT group, no significant differences were observed in OS and EFS among the three subgroups. AML, acute myeloid leukemia; OS, overall survival; EFS, event-free survival; allo-HSCT, allogeneic hematopoietic stem cell transplantation.

FBXO41, *FOXRED2*, *IPO9*, *MCM4*, *MRPS18B*, *SF3B3*, and *ZHX3* as the potential targets of miR-17.

Functional enrichment analysis of DEGs

Functional enrichment analysis was performed to further explore the biological functions of the DEGs associated with miR-107 and miR-17 expression. The Gene Ontology (GO) analysis indicated these DEGs were significantly enriched in the DNA metabolic process, noncoding RNA (ncRNA) metabolic process, nucleobase-containing small molecule metabolic process, regulation of cell cycle

Table 3 Univariate and multivariate analyses in the entire group

Variables	EFS		OS	
	HR (95% CI)	P value	HR (95% CI)	P value
Univariate analyses				
Combination of miR-107 and miR-17		0.022		0.011
Either high *vs.* both low	1.382 (0.900–2.121)	0.140	1.630 (1.014–2.618)	0.043
Both high *vs.* both low	1.816 (1.190–2.771)	0.006	2.048 (1.279–3.279)	0.003
NPM1 (mutated *vs.* wild)	1.259 (0.866–1.832)	0.228	1.206 (0.803–1.812)	0.366
IDH1 (mutated *vs.* wild)	0.996 (0.572–1.734)	0.989	0.855 (0.459–1.594)	0.622
IDH2 (mutated *vs.* wild)	0.837 (0.462–1.517)	0.558	1.004 (0.537–1.876)	0.990
MLL-PTD (mutated *vs.* wild)	1.714 (0.837–3.513)	0.141	1.541 (0.716–3.318)	0.269
NRAS (mutated *vs.* wild)	1.284 (0.692–2.384)	0.428	0.948 (0.462–1.947)	0.885
KRAS (mutated *vs.* wild)	2.010 (0.937–4.312)	0.073	1.777 (0.780–4.047)	0.171
TP53 (mutated *vs.* wild)	2.757 (1.540–4.936)	<0.001	3.809 (2.091–6.937)	< 0.001
Multivariate analyses				
Combination of miR-107 and miR-17		0.036		0.021
Either high *vs.* both low	1.393 (0.905–2.144)	0.132	1.649 (1.026–2.651)	0.039
Both high *vs.* both low	1.744 (1.141–2.666)	0.010	1.923 (1.198–3.087)	0.007
KRAS (mutated *vs.* wild)	2.079 (0.965–4.481)	0.062	1.893 (0.828–4.330)	0.130
TP53 (mutated *vs.* wild)	2.757 (1.528–4.975)	<0.001	3.723 (2.026–6.842)	<0.001

EFS, event-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval.

process, and regulation of chromosome organization. Pathway enrichment analysis revealed the DEGs were mainly enriched in the metabolism of RNA, glycolysis, DNA ionizing radiation (IR)-damage and cellular response via ataxia telangiectasia and Rad3-related (ATR), and E2F mediated regulation of DNA replication (*Figure 6*).

Discussion

In this study, we demonstrated that the overexpression of miR-107 or miR-17 was significantly related to adverse OS and EFS in patients with AML, which could be overcome by allo-HSCT. Patients with high expression levels of both miR-107 and miR-17 had the worst OS and EFS in the entire cohort as well as in the chemotherapy group. We suggest the combined criteria of miR-107 and miR-17 should be regarded as an unfavorable prognosticator for patients with AML, and using these combined criteria might improve risk stratification and patient outcomes by selecting patients suitable for allo-HSCT.

MiR-107 belongs to the miR-15/107 gene group and is involved in multiple physiological processes, including cell cycle, cellular metabolism, stress response, and angiogenesis (14,15). Previous studies indicated the aberrant expression of miR-107 was associated with the prognosis and therapeutic effect of patients with malignant tumors, and as a double-face gene, its role remains controversial in different cancer types. For instance, miR-107 was downregulated in colorectal cancer (16), renal clear cell carcinoma (17), cervical cancer (18), glioma (19), non-small cell lung cancer (20), gastric cancer (21,22), and penile cancer (23), where it acted as a tumor suppressor. On the other hand, miR-107 was upregulated in gastric cancer (24), triple-negative breast cancer (25), penile cancer (23), hepatocellular carcinoma (26), and colorectal cancer (27), where it acted as an oncogene. In the current study, we investigated the prognostic significance of miR-107 in AML for the first time, and the results showed its upregulation was related to poor OS and EFS. Further, this poor prognosis could be overcome by allo-HSCT but not by chemotherapy. Previous studies have reported the

Table 4 Univariate and multivariate analyses in the chemotherapy group

Variables	EFS		OS	
	HR (95% CI)	P value	HR (95% CI)	P value
Univariate analyses				
Combination of miR-107 and miR-17		0.017		0.018
Either high *vs.* both low	1.688 (0.924–3.084)	0.088	1.671 (0.901–3.099)	0.103
Both high *vs.* both low	2.404 (1.317–4.388)	0.004	2.430 (1.313–4.498)	0.005
NPM1 (mutated *vs.* wild)	1.425 (0.860–2.362)	0.169	1.236 (0.733–2.085)	0.427
IDH1 (mutated *vs.* wild)	1.153 (0.464–2.864)	0.759	1.250 (0.502–3.109)	0.632
IDH2 (mutated *vs.* wild)	1.163 (0.555–2.435)	0.689	1.221 (0.582–2.558)	0.597
MLL-PTD (mutated *vs.* wild)	1.107 (0.403–3.036)	0.844	1.231 (0.448–3.383)	0.687
NRAS (mutated *vs.* wild)	1.141 (0.494–2.635)	0.758	1.242 (0.537–2.875)	0.612
KRAS (mutated *vs.* wild)	2.364 (0.943–5.927)	0.066	2.404 (0.960–6.017)	0.061
TP53 (mutated *vs.* wild)	3.486 (1.685–7.212)	< 0.001	3.416 (1.653–7.061)	< 0.001
Multivariate analyses				
Combination of miR-107 and miR-17		0.085		0.105
Either high *vs.* both low	1.532 (0.830–2.827)	0.172	1.513 (0.807–2.835)	0.197
Both high *vs.* both low	2.022 (1.086–3.767)	0.027	2.000 (1.055–3.793)	0.034
KRAS (mutated *vs.* wild)	2.320 (0.905–5.946)	0.080	2.278 (0.884–5.873)	0.088
TP53 (mutated *vs.* wild)	3.057 (1.448–6.454)	0.003	2.976 (1.408–6.289)	0.004

EFS, event-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval.

role of miR-107 in regulating chemo-drug sensitivity among several cancer types, such as colorectal cancer (28), breast cancer (29,30), and non-small cell lung cancer (31,32). In addition, the level of miR-107 could be modulated by small-molecule drugs, including CDK inhibitor SNS-032 (33), all-trans-retinoic acid (34), Agrimonia pilos polysaccharide (35), 6-hydroxydopamine (36), and skullcapflavone I (37). Whether these drugs might improve the efficacy of chemotherapy in AML through regulating miR-107 expression requires further study.

MiR-17, one of the most extensively studied members in the miR-17-92 cluster, also exhibits oncogenic and tumor-suppressive functions depending on the cancer type. For instance, overexpression of miR-17 was associated with poor survival in pancreatic cancer (38), prostate cancer (39), Burkitt lymphoma (40), colorectal cancer (41), esophageal adenocarcinoma (42), and nasopharyngeal carcinoma (43). In contrast, miR-17 was independently associated with a favorable prognosis in triple-negative breast cancer (44) and myelodysplastic syndromes (45). Furthermore, miR-17 plays a dual role as an oncogenic and tumor-suppressor in lung cancer (46). Previous studies reported miR-17 was downregulated in patients with Core Binding Factor (CBF)-AML but upregulated in patients with non-CBF-AML. The ectopic expression of miR-17 induced undifferentiated myeloid cell proliferation (47), whereas its prognostic value in AML is largely unknown. Our findings support the role of miR-17 as an oncogene in patients with AML and suggest that its high expression is associated with poor OS and EFS. Similarly, allo-HSCT might be a safe and feasible therapy for patients with AML with high expression levels of miR-17.

The biological implications of miR-107 and miR-17 were further elucidated by bioinformatics analysis. Among the screened DEGs, 14 and 10 genes were predicted as the potential targets of miR-107 and miR-17, respectively. Based on these candidate target genes, *HMGA1*, *PHB*, *MCM4*, *RHOBTB2*, *PRMT5*, *LRPPRC*, and *VCP* were found to play important roles in leukemia. *HMGA1*, as a key epigenetic switch, was involved in the transformation

Table 5 Univariate and multivariate analyses in the allo-HSCT group

Variables	EFS		OS	
	HR (95% CI)	P value	HR (95% CI)	P value
Univariate analyses				
Combination of miR-107 and miR-17		0.431		0.448
Either high *vs.* both low	1.142 (0.617–2.113)	0.672	1.247 (0.599–2.593)	0.555
Both high *vs.* both low	1.501 (0.803–2.809)	0.203	1.617 (0.767–3.411)	0.207
NPM1 (mutated *vs.* wild)	1.009 (0.576–1.768)	0.975	1.130 (0.591–2.161)	0.711
IDH1 (mutated *vs.* wild)	0.876 (0.430–1.784)	0.715	0.763 (0.322–1.808)	0.539
IDH2 (mutated *vs.* wild)	0.473 (0.171–1.307)	0.149	0.665 (0.204–2.164)	0.498
MLL-PTD (mutated *vs.* wild)	6.032 (2.042–17.816)	0.001	2.738 (0.837–8.962)	0.096
NRAS (mutated *vs.* wild)	1.598 (0.636–4.017)	0.319	0.494 (0.119–2.048)	0.331
KRAS (mutated *vs.* wild)	1.004 (0.244–4.127)	0.996	0.538 (0.074–3.920)	0.541
TP53 (mutated *vs.* wild)	1.643 (0.588–4.590)	0.343	4.217 (1.422–12.503)	0.009
Multivariate analyses				
MLL-PTD (mutated *vs.* wild)	6.300 (2.123–18.695)	<0.001	3.053 (0.927–10.053)	0.066
TP53 (mutated *vs.* wild)	1.786 (0.636–5.014)	0.270	4.538 (1.521–13.540)	0.007

allo-HSCT, allogeneic hematopoietic stem cell transplantation; EFS, event-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval.

of myeloproliferative neoplasms into primary myelofibrosis and AML (48). *PHB*, as a tumor suppressor, was overexpressed in various leukemic cells and participated in cell cycle progression, transcriptional regulation, and cell surface signaling (49). *MCM4*, as a critical regulator of DNA replication, participated in leukemogenesis and was associated with a dismal prognosis of chronic myeloid leukemia (CML) (50,51), while *RHOBTB2*, as an atypical subfamily of Rho guanosine triphosphatases (GTPases), was reported to increase in AML and was related to adverse outcomes (52). *LRPPRC*, as a transcription factor, was involved in imatinib mesylate resistance in CML (53), and *PRMT5*, which belongs to protein arginine methyltransferases, regulated the ATF4 oxidative stress pathway of AML (54). *VCP*, as an abundant molecular chaperone, was enriched in the regulation of autophagy, receptor-mediated endocytosis, and DNA damage repair. A previous study noted that inhibition of *VCP* induced an unfolded protein response and apoptosis of AML cells and might be a potential therapeutic strategy for the disease (55). By performing GO and pathway enrichment analysis, we found the DEGs associated with miR-107 and miR-17 expression were mainly enriched in multiple metabolic processes. Therefore, the gene-expression pattern associated with miR-107 and miR-17 might provide new insights into their biological roles in AML.

To the best of our knowledge, we are the first group to explore the prognostic role of miR-107 in combination with miR-17 in AML. Patients characterized by the concurrence of miR-107^{high} and miR-17^{high} experienced poor survival, but this could be circumvented by allo-HSCT.

There are some limitations in our study. First, the results were obtained in a single cohort, and the study lacked multi-center clinical data to confirm the prognostic significance of miR-107 and miR-17 in AML. Second, the sample quantity was small for this study, and the results need to be verified by expanding its size. Third, the detailed mechanism of miR-107 and miR-17 in AML remains unknown.

Conclusions

The concurrence of high expression levels of miR-107 and miR-17 predicted unfavorable survival in patients with AML. The use of these combined criteria might improve risk stratification and decision-making regarding the optimal regimen for a specific patient with AML.

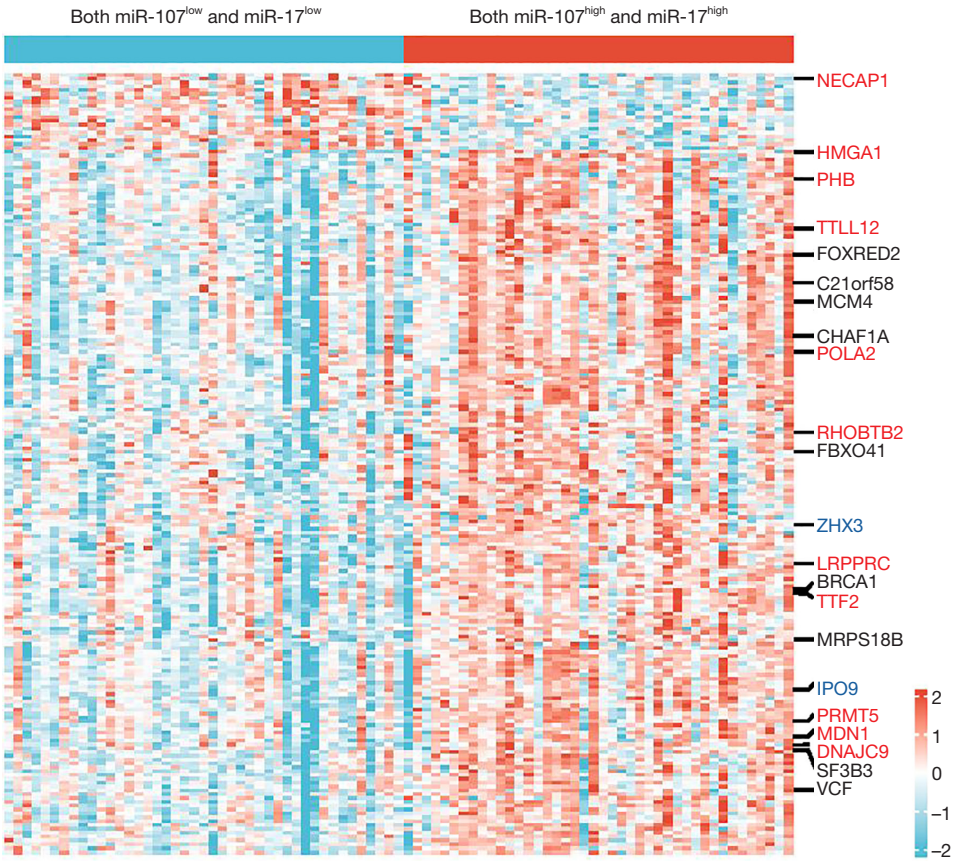

Figure 5 DEGs between patients with AML in both low and both high expression groups. The horizontal axis represents the different patients, and the vertical axis represents DEGs. The genes marked red, black, and blue represent the targets of miR-107, miR-17, and the common targets of miR-107 and miR-17, respectively. DEGs, differentially expressed genes; AML, acute myeloid leukemia.

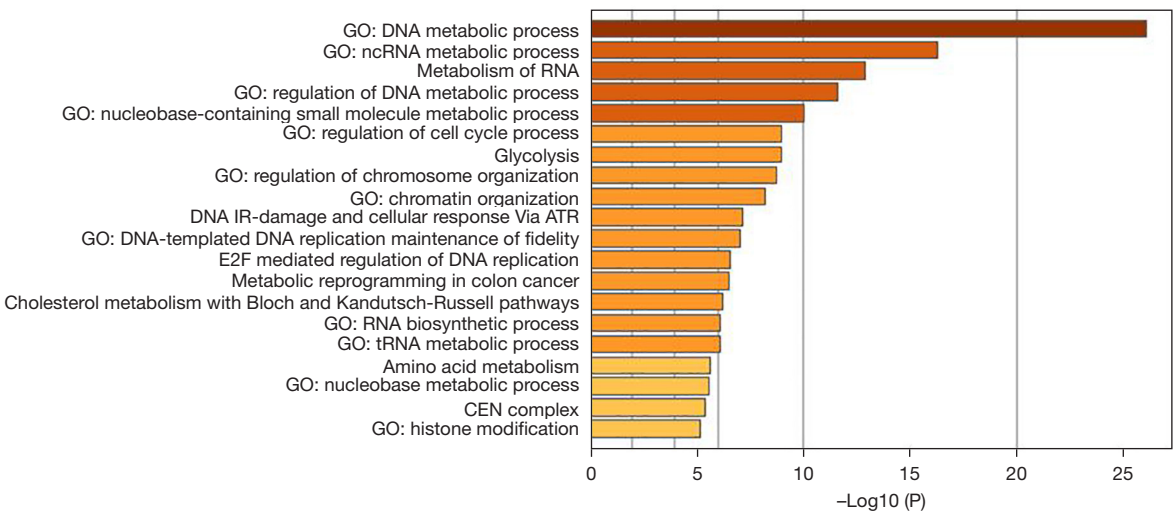

Figure 6 Functional enrichment analysis of DEGs. The horizontal axis represents the enrichment score, and the vertical axis represents the GO and pathway project. DEGs, differentially expressed genes; GO, Gene Ontology; ncRNA, noncoding RNA; IR, ionizing radiation; ATR, ataxia telangiectasia and Rad3-related; tRNA, transfer RNA; CEN, centromere.

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Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2484/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2484/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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