

Research Paper



High expression of MiR-98 is a good prognostic factor in acute myeloid leukemia patients treated with chemotherapy alone

Ning Hu¹, Zhiheng Cheng², Yifan Pang^{3,4}, Hongmian Zhao¹, Li Chen¹, Chao Wang¹, Tong Qin¹, Qianyu Li¹, Yu Han¹, Jinlong Shi^{2,5,6}, Lin Fu^{1,3}

1. Department of Hematology, Huaihe Hospital of Henan University, Kaifeng, 475000, China

- 2. Translational Medicine Center, Huaihe Hospital of Henan University, Kaifeng, 475000, China
- 3. Department of Hematology and Lymphoma Research Center, Peking University, Third Hospital, Beijing, 100191, China
- 4. Department of Medicine, William Beaumont Hospital, Royal Oak, MI 48073, USA
- 5. Department of Biomedical Engineering, Chinese PLA General Hospital, Beijing, 100853, China
- 6. Department of Medical Big Data, Chinese PLA General Hospital, Beijing, 100853, China

Corresponding author: Lin Fu, MD. PhD. Department of Hematology and Lymphoma Research Center, Peking University, Third Hospital, Beijing, 100191, China. E-mail: fulin022@126.com, Tel: +86-10-82267650, Fax: +86-10-82267650. Jinlong Shi, PhD. Department of Biomedical Engineering, Chinese PLA General Hospital, Beijing, 100853, China. E-mail: jinlong_301@163.com, Tel: +86-10-66936921, Fax: +86-10-66936921.

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Abstract

It has been demonstrated that microRNA-98 (miR-98) is dysregulated in multiple types of solid tumors, but its expression and impact in acute myeloid leukemia (AML) is unclear. To explore the prognostic role of miR-98 in AML, 164 AML patients with the miR-98 expression data were extracted from The Cancer Genome Atlas (TCGA) database and enrolled in this study. First, patients were divided into chemotherapy-only (chemotherapy) group and allogeneic hematopoietic stem cell transplant (allo-HSCT) group. Each group was then divided in two groups by the median expression level of miR-98. In chemotherapy group, high miR-98 expression was associated with longer event-free survival (EFS, P = 0.003) and overall survival (OS, P = 0.004), but in allo-HSCT group, EFS and OS were not significantly different between high and low miR-98 expressers. Second, All patients were divided in two groups by the median expression level of miR-98. In low miR-98 expressers, those treated with allo-HSCT had longer EFS (P = 0.001) and OS (P < 0.001) than chemotherapy, but in high miR-98 expressers, survival was independent from treatment modalities. Gene ontology enrichment analysis indicated that the genes associated with miR-98 expression were mainly concentrated in "definitive hemopoiesis", "negative regulation of myeloid cell differentiation" and "signaling pathways regulating pluripotency of stem cells" pathways. In conclusion, our results indicated that high miR-98 expression confers good prognosis in AML patients treated with chemotherapy alone. Patients with low miR-98 expression may benefit from allo-HSCT.

Key words: Acute myeloid leukemia; MiR-98; Allogeneic hematopoietic stem cell transplantation; Chemotherapy; Prognosis

Introduction

The vast genetic heterogeneity is not only characteristic of acute myeloid leukemia (AML)^[1] but also has important prognostic implications. For example, *NPM1* mutation without positive *FLT3-ITD* is a good prognostic factor in cytogenetically normal

AML (CN-AML) ^[2,3], while the latter is a poor prognostic factor ^[4]. *DNMT3A* and *TP53* mutations are both negative prognostic factors in AML ^[5,6]. Double *CEBPA* mutation is associated with favorable prognosis in CN-AML patients ^[7].

MicroRNAs (miRNAs) are short noncoding RNAs that regulate genes post-transcriptionally and play an important role in various physiological and developmental processes such as cell proliferation and differentiation, development, and apoptosis, all of which are frequently affected in cancer [8,9]. Growing number of studies are demonstrating that the dysregulation of miRNAs is associated with the development and progression of many cancers including leukemia, and may provide useful prognostic information [10-13]. For instance, higher levels of miR-155 and lower levels of miR-181a are independently associated with shorter survival in CN-AML patients [14]. MiR-29a and miR-29b can induce apoptosis in AML by targeting apoptosis gene MCL-1 ^[15]. MiR-9 and miR-196b play essential oncogenic roles in mixed lineage leukemia-rearranged AML [16]. High miR-99a expression and low miR-215 expression are associated with worse clinical outcome in AML [17,18].

MiR-98 belongs to the let-7 families that have been shown to be down-regulated in high-risk ovarian cancer, lung cancer, melanoma and other solid tumors ^[19-22]. Previous study found that let-7b and let-7c were tumor suppressors and would be down-regulated in AML with t(8;21) or inv(16) ^[23]. Here, we retrospectively studied the association between miR-98 expression and survival in AML patients to help elucidating its clinical and prognostic implications.

Materials and Methods

Patients

A total of 164 AML patients with miR-98 expression data were identified in The Cancer Genome Atlas (TCGA) database (https://cancergenome.nih.gov/) and enrolled in this study [24]. Ninety patients were treated with chemotherapy alone, and other 74 also received allogeneic hematopoietic stem cell transplant (allo-HSCT). All clinical and molecular information including miR-98 expression levels were publicly accessible from the TCGA website. All patients provided written informed consent; the research was approved by the Human Research Ethics Committee of Washington University. Primary endpoints were event-free survival (EFS) and overall survival (OS). EFS was defined as the time from diagnosis to removal from the study due to the absence of complete remission, relapse or death or was censored at the last follow-up. OS was defined as the time from diagnosis to death or was censored at the last follow-up.

Statistical Analysis

All statistical analyses were performed by SPSS software 20.0 and GraphPad Prism software 5.0. The clinical and molecular characteristics of patients were summarized using descriptive statistics. The Mann-Whitney *U* test and the chi-square test were used to compare continuous and categorical data between the two groups, respectively. The EFS and OS rates were estimated using the Kaplan-Meier method and compared using the log-rank test. Cox proportional hazard models were constructed for uniand multivariate analyses to identify the association between each clinical and molecular variable and survival. For all statistical analyses, P values were two-sided and P < 0.05 was considered significant.

Results

Associations between miR-98 expression and clinical and molecular characteristics of patients

Patients were divided into two groups based on the treatment they received chemotherapy group and allo-HSCT group. Each group was then divided into two groups by the median expression level of miR-98. The clinical and molecular characteristics of each group were detailed in Table 1.

In the chemotherapy group, high miR-98 expressers had lower percentages of bone marrow (BM) blasts (P = 0.048), more good-risk patients (P =0.002) and fewer intermediate-risk patients (P = 0.011) than low expressers. Six patients among the high expressers harbored RUNX1-RUNX1T, whereas it was not found in low expressers (P = 0.026). High expressers had less in NPM1 (P = 0.001) and DNMT3A (P = 0.002) mutations. No significant differences were found in age, gender distribution, WBC counts, peripheral blood (PB) blasts, French-American-British (FAB) classification, frequency of other recurrent genetic mutations (FLT3-ITD, CEBPA, IDH1/IDH2, RUNX1, MLL-PTD, TP53, NRAS/KRAS and TET2) and relapse rate between high and low miR-98 expression groups.

In the allo-HSCT group, high miR-98 expressers had younger (P = 0.043), more poor-risk (P = 0.047), and fewer intermediate-risk patients (P = 0.002) than low expressers. High expressers had less *NPM1* (P <0.001) and *DNMT3A* mutations (P = 0.007). No significant differences were found in gender distribution, BM blasts, FAB classification, karyotypes, frequency of other recurrent genetic mutations (*FLT3-ITD*, *CEBPA*, *IDH1/IDH2*, *RUNX1*, *MLL-PTD*, *NRAS/KRAS*, *TET2* and *TP53*) and relapse rate between high and low miR-98 expression groups.

Table 1. Clinical and molecular characteristics of patients in different treatment groups

High allows arr 450Low allswiss arr 450PHigh allows arr 570arr 570ar	Characteristics	Chemotherapy group			Allo-HSCT group				
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Age/yamp.0%12.80%18.40%18.40%18.40%18.40%18.40%18.4< %0 yamp.		(n = 45)	(n = 45)		(n = 37)	(n = 37)			
Are groups 60)16(1.1)15(3.3)50(8).1)14(6.9)1.112 60 yars16(0.1)15(3.1)7(1.8)15(3.1)12 60 yars10 (60.1)2 (6.9)10 (7.1)15(3.1)15(3.1)1Male2 (6.0)2 (6.9)10 (7.1)15(3.1)15(3.1)15(3.1)1Male2 (6.0)2 (6.9)10 (7.1)15(3.1)15(3.1)15(3.1)11Male2 (6.0)2 (6.9)10 (7.1)15(3.1)15(3.1)1111PM hard10 (6.0)2 (7.1)10 (7.1)15(3.1)111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111<	Age/years, median (range)	66 (22-88)	67 (31-83)	0.781*	45 (18-72)	56 (21-69)	0.043*		
</td <td>Age group/n (%)</td> <td></td> <td></td> <td>0.822§</td> <td></td> <td></td> <td>0.116§</td>	Age group/n (%)			0.822§			0.116§		
2 d) semigration of the semigratio	< 60 years	14 (31.1)	15 (33.3)		30 (81.1)	24 (64.9)			
Gendery(n)	\geq 60 years	31 (68.9)	30 (66.7)		7 (18.9)	13 (35.1)			
Male26/1026/1126/1016/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/1316/13	Gender/n (%)			0.396§			0.159§		
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Notional status2 (44)6 (13.3)0.2668 (81)6 (6.2)0.45790.4579N111 (24.4)9 (20.0)6 (32)11 (27.1)12 (2.4.7)10.0010.07.0)9 (4.3)0.700N40 (0.0)0 (0.0)1 (27.1)1 (2.5.1)10.0010.07.0)9 (4.3.1)0.700M41 (2.2.1)1 (2.2.7.1)1 (0.001 (2.7.1)1 (0.0.1)10.000N50 (0.0)1 (2.2.1)1 (2.2.1)1 (2.7.1)1 (2.7.1)1 (0.0.1)Normal1 (2.2.1)1 (2.7.1)1 (2.7.1)1 (2.7.1)1 (0.0.1)Normal1 (4.0.1)1 (2.5.1)1 (2.7.1)1 (2.7.1)1 (0.0.1)Normal1 (4.0.1)1 (2.7.1)1 (2.7.1)1 (0.0.1)1 (2.7.1)1 (2.7.1)1 (0.0.1)Normal1 (4.0.1)1 (2.7.1)1 (2.7.1)1 (2.7.1)1 (0.0.1)1 (2.7.1)1 (2.7.1)1 (2.7.1)1 (2.7.1)1 (2.7.1)1 (2.7.1)1 (2.7.1)1 (2.7.1)1 (2.7.1)1 (2.7.1)1 (2.7.1)1 (2.7.1)1 (2.7.1)1 (2.7.1)1 (2.7.1)1 (2.7.1)1 (2.7.1)1 (2.7.1)1 (2.7.1)1 (2.7.1)1 (2.7.1)1 (2.7.1)1 (2.7.1)1 (2.7.1)1 (2.7.1)1 (2.7.1)1 (2.7.1)1 (2.7.1)1 (2.7.1)1 (2.7.1)1 (2.7.1)1 (2.7.1)1 (2.7.1)1 (2.7.1)1 (2.7.1)1 (2.7.1)1 (2.7.1)1 (2.7.1)1 (2.7.1)1 (2.7.1)1 (2.7.1)1 (2.7.1)1 (2.7.1)1 (2.7.1)1 (2.7.1)1 (2.7.1)1 (2.7.1)	FAB subtypes/n (%)								
M111 (24)9 (200)0.6121 (28'7)1 (20.7)0.632M214 (31.1)7 (15.6)0.81110.709 (2.4.3)0.709M312 (6.5.7)12 (2.7)10.0010.71 (2.7)1.000M412 (2.5.7)10 (2.7)1 (2.7)1.00010.71 (2.7)1.000M51 (2.2)1 (2.7)1 (2.7)1 (0.00)1 (0.00)1 (0.00)1 (0.00)M61 (2.2)1 (2.7)1 (2.7)1 (0.00)1 (0.00)1 (0.00)1 (0.00)Karyotype/ft/612.71 (2.7)1 (0.00)1 (0.00)1 (0.00)1 (0.00)1 (0.00)Strisony0 (0.0)0 (0.0)0 (0.0)3 (8.1)3 (8.1)1 0.000Strisony0 (0.0)0 (0.0)0 (0.0)3 (8.1)3 (8.1)1 0.0001025/MIN1116 (15.3)1 (2.7)0 (0.0)0 (0.0)1 (2.7)1 (0.00)1025/MIN1116 (15.3)0 (0.0)0 (0.0)1 (2.7)1 (0.0)1025/MIN1116 (15.3)0 (0.0)0 (0.0)1 (2.6)1 (0.0) <td>MO</td> <td>2 (4.4)</td> <td>6 (13.3)</td> <td>0.266§</td> <td>3 (8.1)</td> <td>6 (16.2)</td> <td>0.479§</td>	MO	2 (4.4)	6 (13.3)	0.266§	3 (8.1)	6 (16.2)	0.479§		
N214/117/15.00.08110/27.09.2.3'0.709M30.001.2.71.0.091.2.71.0.09M41.2.6.71.2.0.8.71.0.009.0.1.35.1.5.30.2.55M55.1.1.18.7.6.71.0.091.2.71.0.01.0.09M61.2.21.0.0.91.2.71.0.01.0.00Kryntypén (%)1.2.71.0.2.71.0.001.0.00Normal8.(0.0.76.7.110.3557.18.95.15.50.2.55Complex7.05.05.11.10.3557.18.95.15.50.2.55Strisony0.000.003.613.61.50.2.56Complex7.05.00.002.641.0.271.0.00int(h) (DEP)-MYH116.15.30.002.641.0.271.0.001.022// (DEP)-MYH116.15.30.002.640.000.0541.022// (DEP)-MYH116.15.30.001.0062.641.0.271.0091.022// (DEP)-MYH116.15.30.001.0062.640.000.0541.022// (DEP)-MYH116.15.30.001.0062.640.000.0541.022// (DEP)-MYH116.15.30.001.0062.640.000.0541.022// (DEP)-MYH116.15.30.001.0091.0090.0040.0041.022// (DEP)-MYH116.15.30.001.0090.0040.0040.0041.022// (DEP)-MYH116.15.30.001.009 <td< td=""><td>M1</td><td>11 (24 4)</td><td>9 (20 0)</td><td>0.612§</td><td>11 (29 7)</td><td>12 (32 4)</td><td>0.802\$</td></td<>	M1	11 (24 4)	9 (20 0)	0.612§	11 (29 7)	12 (32 4)	0.802\$		
MS0 (0)0 (0)0 (0)10,71,7,71,7,71,7,71,00°M42,65,710,64,70,0681,273,61,10,058M51,62,21,62,21,0061,270,001,009M61,62,21,64,70,0941,270,001,009M60,00,02,64,40,9941,271,271,009Karyotype/ft%/00,000,00,03,81,11,009Congles7,15,65,11,10,3357,16,8,95,15,10,328S frisony0,000,00,03,81,11,0091,0271,009Int(2)/CPFp-MH116,15,31,02,72,16,21,0091,0271,009Int(2)/CPFp-MH116,15,30,000,0242,16,31,02,71,009Int(2)/CPFp-MH116,15,30,000,0262,141,02,71,009Int(2)/CPFp-MH116,15,30,000,0022,141,02,71,009Int(2)/CPFp-MH116,15,30,000,0022,141,02,71,009Int(2)/CPFP-MH111,12,20,0010,001,271,009Int(2)/CPFP-MH111,12,30,000,002,141,271,009Int(2)/CPFP-MH111,12,30,001,12,71,0091,12,71,009Int(2)/CPFP-MH111,12,30,000,000,000,000,000,000,000,000,000,000,000,000,000,00 <t< td=""><td>M2</td><td>14 (31 1)</td><td>7 (15.6)</td><td>0.081§</td><td>10(270)</td><td>9 (24.3)</td><td>0.790\$</td></t<>	M2	14 (31 1)	7 (15.6)	0.081§	10(270)	9 (24.3)	0.790\$		
N412 (26.7)12 (26.7)1.0009 (24.5)5 (13.5)1.235N55 (11.1)8 (77.6)0.3681 (27)0 (0.0)1.000M70 (0.0)2 (4.4)0.4441 (2.7)1 (2.7)0 (0.0)1.000M70 (0.0)2 (4.4)0.4441 (2.7)1 (2.7)0 (0.0)1.000M70 (0.0)2 (4.4)0.4441 (2.7)1 (2.7)0 (0.0)0.005Strongleyft (%)3 (8.1)3 (8.1)1.0000.0257 (1.5 (8.1)0.000.025S Trisony0 (0.0)0 (0.0)3 (8.1)3 (8.1)1.0000.0541 (2.7)1.00011 (2/2) (M1-RARA0 (0.0)0 (0.0)0 (2.2)2 (5.4)1 (2.7)1.000(153/1) (M1-RARA0 (0.0)0 (0.0)0 (0.0)1 (2.7)1.0001 (2.7)1.000(153/1) (M1-RARA0 (0.0)0 (0.0)0 (0.0)1 (2.7)1.0001 (2.7)1.000(153/1) (M1-RARA1 (2.2)0 (0.0)0 (0.0)1 (2.7)1.0001 (2.7)1.000(153/1) (M1-RARA1 (2.2)0 (0.0)0 (0.0)1 (2.7)1.0001 (2.7)1.000(153/1) (M1-RARA1 (2.2)0 (0.0)1 (2.7)1 (2.0)1 (2.7)1.000(153/1) (M1-RARA1 (2.2)1 (2.2)0 (0.0)1 (2.7)1 (0.0)(153/1) (M1-RARA1 (2.2)1 (2.7)1 (2.7)1 (0.0)(153/1) (M1-RARA1 (2.2)1 (2.7)1 (2.7)1 (2.	M3	0 (0 0)	0 (0 0)	0.001	1 (27)	1 (27)	1 000\$		
msfullfullfullfullfullfullfullfullfullfullM61(2)1(2)1(2)1(00)1(27)1(27)1(27)1(00)1000Karyetyén (#)1(27)1(27)1(27)1(00)1000Karyetyén (#)5(67)0.092*11(27)25(62)0.005*Complex7(15.6)5(11.1)0.535*7(18.9)5(13.5)0.0000.001inv(16) (Chile/MY111613.3)1(2.2)0.1005(13.5)0.00.00.0011/22/ML3(6.7)0.242*2.64.11(2.7)1.000(1/5.7)/PUL-RARA0.000.000.00*1(2.7)1.000(1/5.7)/PUL-RARA0.000.001.00*0.000.00*0.00(1/5.7)/PUL-RARA0.000.00*1.00*0.00*0.00*0.00*(1/5.7)/PUL-RARA0.000.00*1.00*0.00*0.00*0.00*(1/5.7)/PUL-RARA0.000.00*0.00*1.00*0.00*(1/5.7)/PUL-RARA0.000.00*0.00*0.00*0.00*0.00*(1/5.7)/PUL-RARA0.000.00*0.00*0.00*0.00*0.00*(1/5.7)/PUL-RARA0.000.00*0.00*0.00*0.00*0.00*(1/5.7)/PUL-RARA0.00*1.02*0.00*0.00*0.00*0.00*(1/5.7)/PUL-RARA0.00*0.00*0.00*0.00*0.00* </td <td>M4</td> <td>12 (26 7)</td> <td>12 (26 7)</td> <td>1.000§</td> <td>9 (24 3)</td> <td>5 (13 5)</td> <td>0.2358</td>	M4	12 (26 7)	12 (26 7)	1.000§	9 (24 3)	5 (13 5)	0.2358		
M612.212.212.210.00*12.70.001.00*M70.002 (4.4)0.49412.71.001.00*M70.002 (4.4)0.49412.71.2.71.00M70.002 (6.7)0.092*1.1 (2.7)2.1 (2.2)0.05Somplex7 (15.6)5 (1.1)0.53*7.13.50.00.00.054Somplex7 (15.6)0.002 (6.1)3.8.11.00*11(4)/17/17/17/17/17/17/17/17/17/17/17/17/17/	M5	5 (11 1)	8 (17.6)	0.368§	1 (27)	3 (81)	0.6158		
mm leap leap leap leap leap leap leap leap leap Karyotyp/ (%) Complex 7 (15.6) 5 (11.1) 0.55 7 (18.9) 5 (13.5) 0.258 S Tissemy 0 (0.0) 0 (0.0) 3 (8.1) 1 (2.7) 1.000 inv(16) (CBEP-MY111 6 (13.3) 1 (2.2) 0.100 2 (5.4) 1 (2.7) 1.000 (15.7) / PML-RARA 0 (0.0) 0 (0.0) 1 (2.7) 1 (2.7) 1.000 0 (0.0) 0.001 0.026 0 (0.0) 0.001 0.026 (15.7) / PML-RARA 0 (0.0) 0.001 0.002 2 (5.4) 1 (2.7) 1.0004 (15.2) / RML-RARA 0 (0.0) 0.002 2 (5.4) 0 (2.7) 1.0004 (15.2) / RML-RARA 0 (0.0) 0.002 2 (5.4) 1.027 0.001 (15.2) / RML-RARA 0 (0.0) 1.002 2 (5.4) 0.271 0.002 2 (5.4) 0.002 </td <td>M6</td> <td>1(22)</td> <td>1 (2 2)</td> <td>1.000\$</td> <td>1 (2.7)</td> <td>0 (0.0)</td> <td>1 000\$</td>	M6	1(22)	1 (2 2)	1.000\$	1 (2.7)	0 (0.0)	1 000\$		
More (b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b)(b) <td>M7</td> <td>0(0.0)</td> <td>2(4.4)</td> <td>0.494§</td> <td>1(2.7)</td> <td>1(2.7)</td> <td>1.0005</td>	M7	0(0.0)	2(4.4)	0.494§	1(2.7)	1(2.7)	1.0005		
Normal18 (40.0)26 (57.8)0.09211 (29.7)23 (62.2)0.0054Complex7 (15.6)5 (1.1.1)0.5387 (18.9)5 (13.5)0.238S Tissemy0 (0.0)0 (0.0)3 (8.1)10.0010.00inv(16) (C3F)-MY1116 (13.3)1 (2.2)0.1005 (15.3)0 (0.0)0.0541/22/ML3 (6.7)0.2422 (5.4)1 (2.7)1.000(15.7) / PML-RARA0 (0.0)0 (0.0)1 (2.7)1 (2.7)1.000(15.7) / PML-RARA0 (0.0)0 (0.0)0.020 (0.0)1 (2.7)1 (0.0)(15.7) / PML-RARA0 (0.0)0 (0.0)0.020 (0.0)1 (2.7)1 (0.0)(15.7) / PML-RARA0 (0.0)0 (0.0)0.020 (0.0)1 (2.7)1 (0.0)(15.7) / PML-RARA0 (0.0)0 (0.0)0.021 (2.7)1 (2.7)1 (0.0)(15.7) / PML-RARA0 (0.0)0 (0.0)2 (5.4)0 (0.0)6 (5.7)2 (5.4)1 (2.7)1 (0.0)(15.7) / PML-RARA1 (2.2)0 (0.1)0.011 (2.7)1 (0.0)1 (2.7)1 (0.0)(16.7)2 (2.6)1 (2.7)0 (0.0)2 (5.4)1 (2.7)1 (0.0)1 (2.7)1 (0.0)(15.7)1 (2.6)1 (2.7)0 (0.0)2 (7.8)0 (0.0)2 (7.8)0 (0.0)2 (7.8)0 (0.0)(16.7)2 (2.6)1 (2.7)1 (2.7)1 (0.0)1 (2.7)1 (0.0)1 (0.0)1 (0.0)1 (0.0)1 (0.0)1 (0.0)1 (0	Karvotyne/n (%)	0 (0.0)	2 (1.1)	0.1710	1 (2.7)	1 (2.7)	1.0005		
Notinit10 (b5)20 (b7)0.00211 (27.1)21 (12.7)0.003Complex7 (15.6)5 (11.1)0.05547 (15.9)5 (15.5)0.2288 Tirsony0 (0.0)0 (0.0)3 (8.1)3 (8.1)1.00011 (27.1)11 (27.1)1.0001.0102 (5.4)1 (2.7)1.00011 (27.1)7/7.4-0 (0.0)0 (0.0)0.2282 (5.4)1 (2.7)1.00011 (27.1)10.0010 (0.0)0.0011 (2.7)1 (0.000.49311 (27.1)10.0010.0000.0240 (0.0)1 (2.7)1 (0.00(16.27)1 (2.8)0 (0.0)0.0240 (0.0)1 (2.7)1 (0.00(16.27)1 (2.6)1 (2.2)0.0144 (0.8)2 (7.3)0.025Poor1 (4 (3.1)1 (2.5)0.4481 (4.8)2 (7.3)0.025Poor1 (9 (2.2)1 (4.9)1 (2.7)1 (9.1)0.005Poor1 (2.6)1 (2.7	Normal	18 (40 0)	26 (57.8)	0.0026	11 (20.7)	22 (62 2)	0.0058		
Chingex (150) 5 (11.1) 0.000 7 (15.3) 0 (15.3) 0 (20) 0 (20) Sirisony 0 (0.0) 1 (2.2) 0.110 5 (15.3) 0 (0.0) 0 (2.54) 1 (2.7) 1.0009 1/(2,3/)(LL) 3 (6.7) 0 (0.0) 2 (5.4) 1 (2.7) 1.0009 -7/74- 0 (0.0) 0 (0.0) 1 (2.7) 1.0009 (15.3) 0 (0.0) 1 (2.7) 1.0009 (1952)//6CR-ABL1 1 (2.2) 0 (0.0) 0.0264 0 (0.0) 1 (2.7) 1.0009 (1952)//6CR-ABL1 1 (2.2) 0 (0.0) 0.0264 0 (0.0) 1 (2.7) 1.0009 (1952)//6CR-ABL1 1 (2.2) 0 (0.0) 0.0264 0 (0.0) 1 (2.7) 1.0009 (1922)/6CR-ABL1 1 (2.7) 1 (1.5) 0.027 0.0024 0.0024 Cood 1 (2.6,7) 1 (2.3) 0.011 1 (4.04) 8 (2.16) 0.0024 Por 1 (2.7) 1 (2.7) 0.0024 0.0049 0.0049 Negativ	Compley	7 (15.6)	20 (57.8) 5 (11.1)	0.525%	7(180)	5 (12.2)	0.528\$		
6 H300/m 6 (0.0) 6 (0.0) 7 (0.1) 7 (0.1) 1.00.5 114(25)/ML 3 (6.7) 0 (0.0) 2 (5.4) 1 (2.7) 1.00.9 11422/ML 3 (6.7) 0 (0.0) 2 (5.4) 1 (2.7) 1.00.9 11425/ML 0 (0.0) 0 (0.0) 1 (2.7) 1 (2.7) 1 (0.0) 11425/ML 1 (2.2) 0 (0.0) 1 (2.7) 1 (2.7) 1 (0.0) 10(22)/CR-ABL1 1 (2.3) 0 (0.0) 0.0264 0 (0.0) 1 (2.7) 1 (0.00 10(22)/CR-ABL1 1 (2.1) 0 (0.2) 0.148 4 (0.8) 2 (5.4) 0.654 10(82)//RC-ME 10 (2.2) 0.014 4 (0.8) 2 (5.4) 0.654 10(82)//RC-ME 10 (2.2) 1 (4.89 2 (7.5) 0.0026 Poor 1 (2.1) 1 (2.5) 0.489 1 (6.13) 0.025 Poor 6 (13.3) 1 (2.2) 8 (21.6) 2 (5.4) 0.216 Poor 1 (1.5) 2 (4.9) 1 (2.7) 1 (5.1) 1 (6	8 Trisomy	7(13.0)	5(11.1)	0.555%	7(10.9)	2 (8 1)	1.000\$		
n (1,6) (Car)-ATTAL 0 (35) (25) (27) (0,0) (0,0) (1,2) (1,2) (1,2) (1,2) (1,2) (1,0) (1,2) (1,2) (1,2) (1,0) (1,2) (1,2) (1,2) (1,0) (1,2) (1,2) (1,2) (1,2) (1,2) (1,0) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1,2) (1	o Trisoniy	0(0.0)	0(0.0)	0.1105	5 (0.1) E (12 E)	5 (6.1) 0 (0.0)	0.0548		
Info Null. S(b.7) 0.00, 2.03, 1.(2.7) 1.000, 7/7q- 0.00, 0.00, 1.2.7, 1.000, 0.00, 1.2.7, 1.000, (10,57)/PML-RARA 0.00, 0.00, 1.02, 1.2.7, 1.000, 0.435, (10,22)/BCR-ABL1 1.2.2, 0.00, 0.026, 0.00, 1.2.7, 1.000, (16,22)/BCR-ABL1 1.2.2, 0.00, 0.026, 0.00, 1.2.7, 1.000, (16,22)/BCR-ABL1 1.2.2, 0.00, 0.026, 0.00, 1.2.7, 1.000, Chers 0.022, 0.448 0.00, 2.5.4 0.00, 0.002, Intermediate 1.2.2, 1.2.3, 0.002, 6.16.7, 2.5.4, 0.002, Poor 1.4.13, 1.1.2.5, 0.400, 8.2.1, 0.002, 0.002, Poor 6.13, 1.0.2.2, 8.01, 2.0, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000,	11 ₂ 22 /ML	0(13.3)	1(2.2)	0.110s	3(13.3)	0(0.0)	0.034 ^s		
-//4p0 (0.0)3 (b.7)0.2422 (4.3)1 (2.7)1.000(1557)/TML-RARA0 (0.0)0 (0.0)1 (2.7)1 (2.7)1 (2.7)1 (0.0)(1557)/TML-RARA1 (2.2)0 (0.0)0.0260 (0.0)1 (2.7)1 (0.0)(1557)/TML-RARA1 (2.3)0 (0.0)0.0260 (0.0)1 (2.7)1 (0.0)(1521)/RUNNL-RUNNITI6 (13.3)10 (2.2)0.1444 (10.8)2 (5.4)0.674Riskn (%)	7/7-	3 (6.7) 0 (0.0)	0 (0.0)	0.2426	2 (5.4)	1 (2.7)	1.000 ⁹		
It (3.7) Jack Aka (2.7) I (2.7) <thi (2.7)<="" th=""> I (2.7) I (2.7)</thi>	-///Q-	0 (0.0)	3 (6.7) 0 (0.0)	0.2428	2 (5.4)	1 (2.7)	1.000 ⁹		
thy for the form of	t(15;17)/PML-KAKA	0 (0.0)	0 (0.0)	1 000%	1(2.7)	1 (2.7)	1.000s		
theory b (15.5) 0 (00) 0.029 0 (00) 1 (2.7) 1.0009 Others 0 (22.2) 0.144 4 (10.8) 2 (5.4) 0.6748 Riskn (%) 0.6748 Riskn (%) 0.6167 2 (5.4) 0.6748 Riskn (%) 12 (26.7) 1 (2.3) 0.0018 4 (0.8) 2 (5.4) 0.2019 Poor 14 (3.1) 11 (25.6) 0.4069 1 (4.4) 8 (21.6) 0.4079 Prost 0.0025 8 (21.6) 9 (24.3) 0.0025 Negative 6 (13.3) 10 (22.2) 8 (21.6) 9 (24.3) 0.0005 Nutation 7 (15.6) 2 (48.9) 1 (27) 1 (3.006 0.0005 Mutation 7 (15.6) 2 (49.9) 1 (27) 1 (3.006 0.0076 Double mutation 0 (0.0) 0 (0.0) 2 (5.4) 1 (2.7) 0.0076 Mutation 6 (13.3) 19 (4	t(9;22)/ BCR-ABLI	1 (2.2)	0 (0.0)	1.000s	2 (5.4)	0 (0.0)	0.493*		
Others4 (6.9)1 (52)0.14394 (10.8)2 (5.4)0.5439Risk/n (*) </td <td>t(8;21)/ KUINAI-KUINAITI</td> <td>6 (13.3)</td> <td>0 (0.0)</td> <td>0.0268</td> <td>0 (0.0)</td> <td>1 (2.7)</td> <td>1.000s</td>	t(8;21)/ KUINAI-KUINAITI	6 (13.3)	0 (0.0)	0.0268	0 (0.0)	1 (2.7)	1.000s		
KasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasarKasar <th< td=""><td>Others</td><td>4 (8.9)</td><td>10 (22.2)</td><td>0.144^{s}</td><td>4 (10.8)</td><td>2 (5.4)</td><td>0.674s</td></th<>	Others	4 (8.9)	10 (22.2)	0.144^{s}	4 (10.8)	2 (5.4)	0.674s		
Cood 12 (26.) 1 (2.) 0.002 b 6 (16.7) 2 (5.4) 0.23 b Poor 14 (31.1) 11 (25.6) 0.480 16 (44.4) 8 (21.6) 0.047 ³ Poor 6 (13.3) 10 (22.2) 8 (21.6) 9 (24.3) 0.78 ³ Positive 6 (13.3) 10 (22.2) 8 (21.6) 9 (24.3) 0.0005 Negative 39 (86.7) 35 (77.8) 29 (78.4) 28 (75.7) 0.0005 Nutation 7 (15.6) 22 (48.9) 1 (2.7) 19 (51.4) 0.0005 Wildtype 38 (84.0) 23 (51.1) 36 (73.3) 18 (48.6) 0.0055 CEBPA/n(%)		12 (0(5)	1 (0.0)	0.000		2 (5 1)	0.0(1)		
Internetiate 19 (42.2) 3 1 (7.1) 0.01 is 14 (88.9) 27 (7.3) 0.0029 Poor 14 (31.1) 11 (25.6) 0.4490 16 (44.4) 8 (21.6) 0.0474 FLT3-ITD/n (%) . 0.2708 . 0.7825 Positive 6 (13.3) 10 (22.2) 8 (21.6) 9 (24.3) NPMI/n (%) . 0.001s 2 (75.4) 2 (75.4) Nutation 7 (15.6) 2 (2 (48.9) 1 (27.1) 19 (51.4) Wildtype 3 (8 (4.4) 2 (51.1) 3 (6 (97.3) 18 (48.6) CEBPA/n (%) . . 0.007 . . Ouble mutation 0 (0.0) 0 (0.0) 2 (54.4) 1 (2.7) . Double mutation 0 (0.0) 0 (0.0 2 (54.4) 1 (2.7) . NMT3A/n (%) 0.007 Wildtype 3 (95.6) 4 (97.8) . 3 (80.2) Duble mutat	Good	12 (26.7)	1 (2.3)	0.002\$	6 (16.7)	2 (5.4)	0.261%		
Poor 14 (31,1) 11 (25,6) 0.480 16 (44.4) 8 (21,6) 0.004 ³ PLT3-ITD/n (%) 0.2708 29 (84.0) 29 (85.7) 29 (84.0) 28 (75.7) 29 (84.0) 28 (75.7) 0.008 Negative 39 (85.7) 35 (77.8) 29 (78.4) 28 (75.7) 0.008 Mutation 7 (15.6) 22 (48.9) 1 (2.7) 19 (51.4) 0.0008 Wildtype 38 (84.0) 23 (51.1) 36 (97.3) 18 (48.6) 3058 Single mutation 0 (0.0) 0.0578 4 (10.8) 1 (2.7) 9 (51.0) Double mutation 0 (0.0) 0 (0.0) 2 (54.4) 1 (2.7) 0.0078 Mutation 0 (0.0) 0 (57.8) 31 (83.8) 35 (94.6) 0 Double mutation 0 (0.0) 2 (57.8) 33 (89.2) 2 (62.7) 0.0078 Mutation 11 (24.4) 5 (11.1) 6 (16.2) 12 (32.4) 10.008 Mutation 11 (24.4) 5 (11.1) 6 (16.2) 12 (32.4) 10.008	Intermediate	19 (42.2)	31 (72.1)	0.0119	14 (38.9)	27 (73.0)	0.002\$		
PL13-11/p (%) 0 (22.) 8 (21.6) 9 (24.3) Negative 39 (86.7) 35 (77.8) 29 (78.4) 28 (75.7) NPM1/p (%) - 0.001 28 (75.7) 0.001 NPM1/p (%) - 0.012 10 (2.7) 19 (51.4) Wildtype 38 (84.4) 23 (51.1) 36 (97.3) 18 (48.6) 0.005 CEBP A/n (%) - 0.557 - 0.305 (51.6) Single mutation 2 (4.4) 1 (2.2) 4 (10.8) 1 (2.7) Double mutation 0 (0.0) 2 (54.4) 1 (2.7) - Mutation 6 (13.3) 19 (42.2) 4 (10.8) 3 (59.6) Mutation 6 (13.3) 19 (42.2) 4 (10.8) 2 (36.2) Mutation 6 (13.3) 19 (42.2) 4 (10.8) 2 (36.2) Mutation 1 (24.4) 5 (11.1) 6 (16.2) 2 (32.4) - Mutation 1 (24.4) 5 (11.1) 6 (16.2) 2 (32.4) - - Mutation 1 (24.4) 5 (11.1) 6 (16.2) 2 (32.4) - - - <t< td=""><td>Poor</td><td>14 (31.1)</td><td>11 (25.6)</td><td>0.480s</td><td>16 (44.4)</td><td>8 (21.6)</td><td>0.047%</td></t<>	Poor	14 (31.1)	11 (25.6)	0.480s	16 (44.4)	8 (21.6)	0.047%		
Positive 6 (13.3) 10 (22.2) 8 (21.6) 9 (24.3) Negative 39 (86.7) 35 (77.8) 29 (78.4) 28 (75.7) NPMI/n (%) 0001 29 (78.4) 28 (75.7) 00005 Mutation 7 (15.6) 22 (48.9) 1 (27.7) 19 (51.4) 00005 Wildtype 38 (84.4) 23 (51.1) 36 (97.3) 18 (48.6) 0005 CBP4/n (%) 000.0 2 (54.0) 1 (27.7) 00356 Single mutation 2 (44.9) 1 (2.2) 4 (10.8) 1 (2.7) 0007^3 Nutation 2 (49.5) 4 (97.8) 31 (83.8) 35 (94.6) 0007^3 Mutation 9 (86.7) 2 (62.5) 33 (89.2) 23 (62.2) 0007^3 Mutation 11 (24.0 5 (11.1) 6 (16.2) 12 (32.4) 0005 Mutation 14 (75.8) 25 (67.6) 0005 0005 0005 Mutation 4 (98.9) 3 (89.2) 3 (89.2) 0005 0005 Mutation 4 (99.1) 33 (89.2) 0005 00005 0005 0005	FL13-11D/n (%)	((2		0.270§		0 (0 (0)	0.782§		
Negative 39 (8.7) 39 (7.8) 29 (8.4) 28 (5.7) NPMI/n (%) 0.0015 0.0015 0.0006 Mutation 7 (15.6) 22 (48.9) 1 (2.7) 19 (51.4) Wildtype 38 (84.4) 23 (51.1) 36 (97.3) 18 (48.6) 0.0056 CEBPA/n (%) 0.557 0.0057 Single mutation 0 (0.0) 0 (0.0) 2 (5.4) 1 (2.7) Double mutation 0 (0.0) 0 (0.0) 2 (5.4) 1 (2.7) Wild type 43 05.6) 4 (07.8) 31 (83.8) 35 (94.6) DNMT3A/n (%) (0.0) 0 (0.0) 2 (5.4) 1 (2.7) 0.0075 Wild type 39 (86.7) 2 (67.8) 31 (83.8) 25 (62.2) 0.0075 Wild type 39 (86.7) 2 (67.8) 33 (89.2) 23 (62.2) 0.0145 Wild type 39 (86.7) 4 (10.8) 1 (2.24) 10.0145 Wild type 34 (75.6) 4 (10.8) 3 (80.2) 2 (67.6) 0.0145 Wild type 4 (10.1) 3 (80.2) 3 (80.2) 2 (67.6) 0.0056	Positive	6 (13.3)	10 (22.2)		8 (21.6)	9 (24.3)			
NPATIP (%) 0.0019 0.0019 0.00019 Witation 7 (15.6) 22 (48.9) 1 (2.7) 19 (51.4) Wildtype 38 (84.4) 2 (51.1) 36 (97.3) 18 (48.6) CEBP (m (%) 0.00.0 2 (4.10.8) 1 (2.7) 0.005 Single mutation 0 (0.0) 0 (0.0) 2 (5.4) 1 (2.7) 0.007 Wild type 43 (95.6) 44 (97.8) 31 (83.8) 35 (94.6) 0.007 DNMT3A/n (%) $0.00.0$ 2 (5.7) 33 (89.2) 23 (62.2) 0.007 Wild type 39 (86.7) 2 (6 (7.8) 33 (89.2) 23 (62.2) 0.007 Mutation 11 (24.4) 5 (11.1) 6 (16.2) 12 (32.4) 0.008 Mutation 11 (24.4) 5 (11.1) 6 (16.2) 12 (32.4) 0.008 Mutation 4 (89.7) 4 (08.8) 31 (83.8) 25 (67.6) 1.008 Mutation 4 (89.7) 4 (0.8) 4 (10.8) 1.0018 Mutation 4 (89.7) 4 (89.7) 3 (89.2) 3 (89.2) 3 (89.2) 3 (89.2) 3 (89.2) 3 (89.2)<	Negative	39 (86.7)	35 (77.8)	0.0014	29 (78.4)	28 (75.7)	0.0004		
Mutation 7 (15.6) 22 (48.9) 1 (2.7) 19 (3.4) Wildtype 38 (84.4) 23 (51.1) 36 (97.3) 18 (48.6) CEBPA/n (%)	<i>NPM1/n</i> (%)		()	0.001\$. ()		0.000§		
Wildtype 38 (84.4) 23 (51.1) 36 (97.3) 18 (48.6) CEBPA/n (%)	Mutation	7 (15.6)	22 (48.9)		1 (2.7)	19 (51.4)			
CEBP (n (%) 0.557% 0.305% Single mutation 2 (4,4) 1 (2,2) 4 (10.8) 1 (2,7) Wild type 43 (95.6) 4 (97.8) 31 (83.8) 35 (94.6) DNMTSA/n (%) 0.00^{5} 0.00^{2} 0.00^{5} 0.00^{7} Mutation 6 (13.3) 19 (42.2) 4 (10.8) 14 (37.8) Wild type 39 (86.7) 26 (57.8) 33 (89.2) 26 (2.2) IDHI/IDH2/n (%) 0.00^{98} 21 (23.24) 0.00^{48} Wild type 34 (75.6) 48 (99.1) 6 (16.2) 12 (32.4) Wild type 34 (75.6) 48 (99.1) 6 (16.2) 12 (32.4) Wild type 34 (75.6) 48 (99.1) 31 (83.8) 26 (57.6) Mutation 14 (9.1.1) 10.008 10 (2.3) 10009 Mutation 4 (9.9) 4 (10.8) 10.008 10009 Mutation 4 (9.9.1) 4 (9.1.1) 3 (80.2) 3 (89.2) 0.618 Presence 3 (67.7) 2 (4.4) 3 (81.1)	Wildtype	38 (84.4)	23 (51.1)		36 (97.3)	18 (48.6)			
Single mutation 2 (4.4) 1 (2.2) 4 (10.8) 1 (2.7) Double mutation 0 (0.0) 0 (0.0) 2 (5.4) 1 (2.7) Wild type 43 (95.6) 44 (97.8) 31 (83.8) 35 (94.6) DNMT3A/n (%) 0.002^{5} 0.002^{5} 0.002^{5} 0.007^{5} Mutation 6 (13.3) 19 (42.2) 4 (10.8) 14 (37.8) Wild type 39 (86.7) 26 (57.8) 33 (89.2) 23 (62.2) DHI/IDH2/n (%) 0.009^{5} 31 (83.8) 12 (32.4) 0.104^{5} Wild type 34 (75.6) 40 (88.9) 31 (83.8) 25 (67.6) 0.104^{5} Wild type 34 (75.6) 40 (88.9) 31 (83.8) 25 (67.6) 0.009^{5} Mutation 14 (91.1) 41 (91.1) 33 (89.2) 0.009^{5} 0.009^{5} Mutation 4 (9.9) 4 (49.9) 34 (90.6) 34 (91.9) $0.6 (97.3)$ 0.615^{5} Mutation 4 (9.3) 4 3 (95.6) 0.009^{5} 0.409^{5} 0.409^{5} NRAS/KRAS/n (%) 5 (11.1) 2 (54.1) 32 (86.5) 0.409	CEBPA/n (%)			0.557§			0.305§		
Double mutation0 (0.0)0 (0.0)2 (5.4)1 (2.7)Wild type49 (5.6)41 (97.8)31 (83.8)35 (94.6)DNMT34n (%) 0.007^8 0.007^8 0.007^8 0.007^8 Mutation6 (13.3)19 (42.2)4 (10.8)14 (37.8)Wild type39 (86.7)26 (57.8)33 (89.2)23 (62.2)IDH/IDH2/n (%) 0.098^8 31 (83.8)25 (67.6)Mutation11 (24.4)5 (11.1)6 (16.2)12 (32.4)Wild type34 (75.6)40 (88.9)31 (83.8)25 (67.6)RUNX1/n (%) 1.000^8 4 (10.8)4 (10.8)1.0008Mutation4 (8.9)4 (8.9)4 (10.8)4 (10.8)Wild type4 (8.9)4 (10.8)4 (10.8)1.0008Mutation4 (91.1)33 (89.2)0.6158Presence3 (6.7)2 (4.4)3 (8.1)1 (2.7)Presence3 (6.7)2 (4.4)3 (8.1)1 (2.7)Absence42 (93.3)43 (95.6)34 (91.9)36 (97.3)NRAS/KRAS/n (%) 0.345^8 0.345^8 0.430^8 Wutation8 (18.2)5 (11.1)2 (5.4)5 (13.5)Wild type36 (81.8)40 (88.9)35 (94.6) 0.008^8 Mutation6 (13.3)6 (13.3)2 (5.4) 0.008^8 TET2/n (%) 0.008^8 35 (94.6) 0.008^8 0.008^8 Wild type39 (86.7)35 (94.6) 0.008^8 0.008^8 Mutation6 (13.3)6 (13.3)2	Single mutation	2 (4.4)	1 (2.2)		4 (10.8)	1 (2.7)			
Wild type 43 (95.6) 44 (97.8) 31 (83.8) 35 (94.6) DNMT3A/n (%) 0.0028 0.0078 Mutation 6 (13.3) 19 (42.2) 4 (10.8) 14 (37.8) 0.0078 Wildtype 39 (86.7) 26 (57.8) 33 (89.2) 23 (62.2) 0.1048 IDHI/IDH2/n (%) 0.00988 0.1048 Wildtype 34 (75.6) 40 (88.9) 31 (83.8) 25 (67.6) 1.0008 RUNXI/n (%) 1.0008 1.0008 Wildtype 4 (8.9) 4 (10.8) 4 (10.8) 4 (10.8) Wildtype 4 (8.9) 4 (8.9) 4 (10.8) 4 (10.8) 1.0008 Wildtype 4 (8.9) 4 (10.8) 4 (10.8) 4 (10.8) 1.0008 Mutation 4 (8.9) 4 (92.3) 33 (89.2) 33 (89.2) 33 (89.2) 33 (89.2) Mutation 4 (8.9) 4 (92.3) 34 (91.9) 33 (89.2) 33 (89.2) 33 (89.2) Mutation 8 (18.2) 5 (11.1) 2 (5.4) 3 (80.2) 33 (89.2) 33 (89.2) <td>Double mutation</td> <td>0 (0.0)</td> <td>0 (0.0)</td> <td></td> <td>2 (5.4)</td> <td>1 (2.7)</td> <td></td>	Double mutation	0 (0.0)	0 (0.0)		2 (5.4)	1 (2.7)			
DNMT3A/n (%) 0.002^{g} 0.002^{g} 0.007^{g} Mutation 6 (13.3) 19 (42.2) 4 (10.8) 14 (37.8) Wildtype 39 (86.7) 26 (57.8) 33 (89.2) 23 (62.2) DIHI/IDH2/n (%) 0.008 ^g 0.008 ^g 0.104 ^g Mutation 11 (24.4) 5 (11.1) 6 (16.2) 12 (32.4) Wildtype 34 (75.6) 40 (88.9) 31 (83.8) 25 (67.6) RUNX1/n (%) 1.0008 4 (10.8) 4 (10.8) 1.0008 Mutation 4 (8.9) 4 (8.9) 4 (10.8) 3 (89.2) 30 (89.2) Mutation 4 (8.9) 4 (8.9) 4 (10.8) 4 (10.8) 1.0008 MLL-PTD/n (%) 1.0008 4 (10.8) 4 (10.8) 6 (15.3) Presence 3 (6.7) 2 (4.4) 3 (8.1) 1 (2.7) Absence 4 (2 (93.3) 43 (95.6) 34 (91.9) 36 (97.3) Mutation 8 (18.2) 5 (11.1) 2 (5.4) 3 (80.1) 1 (2.7) Mutation 6 (13.3) 6 (13.3) 2 (5.4) 3 (80.1) 1 (2.7)	Wild type	43 (95.6)	44 (97.8)		31 (83.8)	35 (94.6)			
Mutation $6 (13.3)$ $19 (42.2)$ $4 (10.8)$ $14 (37.8)$ Wildtype $39 (86.7)$ $26 (57.8)$ $33 (89.2)$ $23 (c2.)$ IDHI/IDH2/n (%) 0.0988 0.0988 $12 (32.4)$ 0.1048 Wildtype $34 (75.6)$ $40 (88.9)$ $31 (83.8)$ $25 (67.6)$ RUNX1/n (%) 10008 $12 (32.4)$ 1.0008 $10 (10.8)$ $12 (32.4)$ Mutation $4 (8.9)$ $40 (88.9)$ $31 (83.8)$ $25 (67.6)$ Mutation $4 (8.9)$ $4 (8.9)$ $4 (10.8)$ $4 (10.8)$ Wildtype $41 (91.1)$ $33 (89.2)$ $36 (92.2)$ Mutation $4 (8.9)$ $4 (9.9)$ $4 (10.8)$ $4 (10.8)$ Wildtype $4 (29.3)$ $4 (9.9)$ $3 (81.2)$ $1 (2.7)$ Absence $2 (93.3)$ $43 (95.6)$ $34 (91.9)$ $36 (97.3)$ NRAS/KRAS/n (%) 0.345^{5} 0.430^{5} 0.430^{5} Mutation $8 (18.2)$ $5 (11.1)$ $2 (5.4)$ $5 (13.5)$ Wildtype $36 (81.8)$ $40 (88.9)$ $35 (94.6)$ $2 (86.5)$ TET2/n (%) 1.000^{5} 1.000^{5} 1.000^{5} Mutation $6 (13.3)$ $6 (13.3)$ $2 (5.4)$ $2 (5.4)$ Wildtype $39 (86.7)$ $35 (94.6)$ 1.000^{5} TET2/n (%) 0.748^{5} 0.748^{5} 1.000^{5} Mutation $6 (13.3)$ $5 (11.1)$ $2 (5.4)$ $2 (5.4)$	DNMT3A/n (%)			0.002§			0.007§		
Wildtype39 (86.7)26 (57.8)33 (89.2)23 (62.2)IDH/IDH2/n (%) 0.098^{8} 0.098^{8} 0.104^{8} Mutation11 (24.4)5 (11.1)6 (16.2)12 (32.4)Wildtype34 (75.6)40 (88.9)31 (83.8)25 (67.6)Mutation4 (8.9)1.0008 $1 (0.8)$ 1.000^{8} Mutation4 (8.9)4 (8.9)4 (10.8)4 (10.8)Wildtype41 (91.1)41 (91.1)33 (89.2)33 (89.2)MLL-PTD/n (%) $1 (2.7)$ 0.615^{8} Presence3 (6.7)2 (4.4)3 (8.1)1 (2.7)Absence4 (93.3)43 (95.6)34 (91.9)36 (97.3)Mutation8 (18.2)5 (11.1) $2 (5.4)$ 0.430^{8} Mutation6 (13.3)6 (13.3) $2 (5.4)$ 1.000^{8} Mutation6 (13.3)6 (13.3) $2 (5.4)$ $2 (5.4)$ Mutation6 (13.3) $5 (11.1)$ $2 (5.4)$ $2 (5.4)$	Mutation	6 (13.3)	19 (42.2)		4 (10.8)	14 (37.8)			
IDH1/IDH2/n (%) 0.0988 0.0988 0.1048 Mutation 11 (24.4) 5 (11.1) 6 (16.2) 12 (32.4) Wildtype 34 (05.6) 31 (83.8) 25 (67.6) RUNX1/n (%) 1.0008 4 (10.8) 25 (67.6) Mutation 4 (8.9) 4 (10.8) 4 (10.8) Wildtype 41 (91.1) 33 (89.2) 33 (89.2) MLL-PTD/n (%) 1.0008 4 (10.8) 4 (10.8) Presence 3 (6.7) 2 (4.4) 3 (8.1) 1 (2.7) Absence 42 (93.3) 43 (95.6) 34 (91.9) 36 (97.3) Mutation 8 (18.2) 5 (11.1) 2 (5.4) 5 (13.5) Mutation 8 (18.2) 5 (11.1) 2 (5.4) 5 (86.5) TET2/n (%) 1.0008 1.0008 1.0008 TET2/n (%) 1.0008 2 (5.4) 1.0008 Wildtype 39 (86.7) 39 (86.7) 35 (94.6) 35 (94.6) Wildtype 39 (86.7) 39 (86.7) 35 (94.6) 1.0008 Mutation 6 (13.3) 5 (11.1) 2 (5.4) 1.0008 </td <td>Wildtype</td> <td>39 (86.7)</td> <td>26 (57.8)</td> <td></td> <td>33 (89.2)</td> <td>23 (62.2)</td> <td></td>	Wildtype	39 (86.7)	26 (57.8)		33 (89.2)	23 (62.2)			
Mutation11 (24.4)5 (11.1)6 (16.2)12 (32.4)Wildtype34 (75.6)40 (88.9)31 (83.8)25 (67.6)RUNX1/n (%)1.0008Mutation4 (8.9)4 (8.9)4 (10.8)Wildtype41 (91.1)33 (89.2)33 (89.2)MLL-PTD/n (%)1.000833 (89.2)33 (89.2)MLL-PTD/n (%)1.00080.6158Presence3 (6.7)2 (4.4)3 (8.1)1 (2.7)Absence42 (93.3)43 (95.6)34 (91.9)36 (97.3)Mutation8 (18.2)5 (11.1)2 (5.4)5 (13.5)Mutation8 (18.2)5 (11.1)2 (5.4)5 (13.5)Wildtype36 (81.8)40 (88.9)35 (94.6)32 (86.5)TET2/n (%)1.00081.00081.0008Mutation6 (13.3)6 (13.3)2 (5.4)2 (5.4)Mutation6 (13.3)5 (11.1)2 (5.4)1.0008Mutation6 (13.3)<	<i>IDH1/IDH2/n</i> (%)			0.098§			0.104§		
Wildtype $34 (75.6)$ $40 (88.9)$ $31 (83.8)$ $25 (67.6)$ RUNX1/n (%) 1.000^8 1.000^8 1.000^8 1.000^8 Mutation $4 (8.9)$ $4 (8.9)$ $4 (10.8)$ $4 (10.8)$ Wildtype $41 (91.1)$ $41 (91.1)$ $33 (89.2)$ $33 (89.2)$ MLL-PTD/n (%) 1.000^8 0.615^8 Presence $3 (6.7)$ $2 (4.4)$ $3 (8.1)$ $1 (2.7)$ Absence $42 (93.3)$ $43 (95.6)$ $34 (91.9)$ $36 (97.3)$ NRAS/KRAS/n (%) 0.345^8 0.430^8 Mutation $8 (18.2)$ $5 (11.1)$ $2 (5.4)$ $5 (13.5)$ Wildtype $36 (81.8)$ $40 (88.9)$ $35 (94.6)$ $32 (86.5)$ TET2/n (%) 1.000^8 1.000^8 1.000^8 Mutation $6 (13.3)$ $6 (13.3)$ $2 (5.4)$ $2 (5.4)$ Mutation $6 (13.3)$ $5 (11.1)$ $2 (5.4)$ $2 (5.4)$ Mutation $6 (13.3)$ $5 (11.1)$ $2 (5.4)$ $2 (5.4)$	Mutation	11 (24.4)	5 (11.1)		6 (16.2)	12 (32.4)			
RUNX1/n (%) 1.0008 1.0008 1.0008 Mutation 4 (8.9) 4 (8.9) 4 (10.8) 4 (10.8) Wildtype 41 (91.1) 33 (89.2) 33 (89.2) MLL-PTD/n (%) 1.0008 0.6158 Presence 3 (6.7) 2 (4.4) 3 (8.1) 1 (2.7) Absence 42 (93.3) 43 (95.6) 34 (91.9) 36 (97.3) NRAS/KRAS/n (%) 0.345^{8} 0.4308 Mutation 8 (18.2) 5 (11.1) 2 (5.4) 5 (13.5) Wildtype 36 (81.8) 40 (88.9) 35 (94.6) 32 (86.5) TET2/n (%) 1.0008 1.0008 1.0008 1.0008 Mutation 6 (13.3) 6 (13.3) 2 (5.4) 3 (94.6) Mutation 6 (13.3) 6 (13.3) 2 (5.4) 3 (94.6) Mutation 6 (13.3) 6 (13.3) 35 (94.6) 35 (94.6) Mutation 6 (13.3) 5 (11.1) 2 (5.4) 2 (5.4) Mutation 6 (13.3) 5 (11.1) 2 (5.4) 2 (5.4)	Wildtype	34 (75.6)	40 (88.9)		31 (83.8)	25 (67.6)			
Mutation 4 (8.9) 4 (8.9) 4 (10.8) 4 (10.8)Wildtype 41 (91.1) 33 (89.2) 33 (89.2)MLL-PTD/n (%) 1.000^8 0.615^8 Presence 3 (6.7) 2 (4.4) 3 (8.1) 1 (2.7)Absence 42 (93.3) 43 (95.6) 34 (91.9) 36 (97.3)NRAS/KRAS/n (%) 0.345^8 0.430^8 Mutation 8 (18.2) 5 (11.1) 2 (5.4) 5 (13.5)Wildtype 36 (81.8) 40 (88.9) 35 (94.6) 32 (86.5)TET2/n (%) 1.000^8 1.000^8 1.000^8 1.000^8 Mutation 6 (13.3) 6 (13.3) 2 (5.4) 35 (94.6)TP53/n (%) 0.748^8 0.748^8 0.748^8 1.000^8 Mutation 6 (13.3) 5 (11.1) 2 (5.4) 1.000^8	RUNX1/n (%)			1.000§			1.000§		
Wildtype41 (91.1)41 (91.1)33 (89.2)33 (89.2)MLL-PTD/n (%)1.00080.6158Presence3 (6.7)2 (4.4)3 (8.1)1 (2.7)Absence42 (93.3)43 (95.6)34 (91.9)36 (97.3)NRAS/KRAS/n (%)0.34580.4308Mutation8 (18.2)5 (11.1)2 (5.4)5 (13.5)Wildtype36 (81.8)40 (88.9)35 (94.6)32 (86.5)TET2/n (%)1.0008Mutation6 (13.3)6 (13.3)2 (5.4)2 (5.4)Mutation6 (13.3)6 (13.3)2 (5.4)35 (94.6)TP53/n (%)0.7488Mutation6 (13.3)5 (11.1)2 (5.4)2 (5.4)	Mutation	4 (8.9)	4 (8.9)		4 (10.8)	4 (10.8)			
MLL-PTD/n (%) 1.000 [§] 0.615 [§] Presence 3 (6.7) 2 (4.4) 3 (8.1) 1 (2.7) Absence 42 (93.3) 43 (95.6) 34 (91.9) 36 (97.3) NRAS/KRAS/n (%) 0.345 [§] Mutation 8 (18.2) 5 (11.1) 2 (5.4) 5 (13.5) Wildtype 36 (81.8) 40 (88.9) 35 (94.6) 32 (86.5) TET2/n (%) 1.000 [§] Mutation 6 (13.3) 6 (13.3) 2 (5.4) 2 (5.4) Mutation 6 (13.3) 39 (86.7) 35 (94.6) 35 (94.6) TP53/n (%) 0.748 [§] Mutation 6 (13.3) 5 (11.1) 2 (5.4) 1.000 [§] Mutation 6 (13.3) 6 (13.3) 2 (5.4) 1.000 [§] Mutation 6 (13.3) 5 (11.1) 2 (5.4) 1.000 [§]	Wildtype	41 (91.1)	41 (91.1)		33 (89.2)	33 (89.2)			
Presence3 (6.7)2 (4.4)3 (8.1)1 (2.7)Absence42 (93.3)43 (95.6)34 (91.9)36 (97.3)NRAS/KRAS/n (%) 0.345^{s} 0.430^{\text{s}}Mutation8 (18.2)5 (11.1)2 (5.4)5 (13.5)Wildtype36 (81.8)40 (88.9)35 (94.6)32 (86.5)TET2/n (%) 1.000^{s} 1.000^{s} 1.000^{s} Mutation6 (13.3)6 (13.3)2 (5.4)2 (5.4)Wildtype39 (86.7)39 (86.7)35 (94.6) $35 (94.6)$ TP53/n (%) 0.748^{s} 1.000^{s} 1.000^{s} Mutation6 (13.3)5 (11.1)2 (5.4) $2 (5.4)$	MLL-PTD/n (%)			1.000§			0.615§		
Absence42 (93.3)43 (95.6) $34 (91.9)$ $36 (97.3)$ NRAS/KRAS/n (%)0.3458 0.4308 Mutation8 (18.2)5 (11.1)2 (5.4)5 (13.5)Wildtype36 (81.8)40 (88.9)35 (94.6)32 (86.5)TET2/n (%)1.0008Mutation6 (13.3)6 (13.3)2 (5.4)2 (5.4)Wildtype39 (86.7)39 (86.7)35 (94.6)35 (94.6)TP53/n (%)0.7488Mutation6 (13.3)5 (11.1)2 (5.4)2 (5.4)	Presence	3 (6.7)	2 (4.4)		3 (8.1)	1 (2.7)			
NRA5/KRA5/n (%) 0.345° 0.430° Mutation 8 (18.2) 5 (11.1) 2 (5.4) 5 (13.5) Wildtype 36 (81.8) 40 (88.9) 35 (94.6) 32 (86.5) <i>TET2/n</i> (%) 1.000 ⁸ 1.000 ⁸ 1.000 ⁸ Mutation 6 (13.3) 6 (13.3) 2 (5.4) 2 (5.4) Wildtype 39 (86.7) 39 (86.7) 35 (94.6) 35 (94.6) <i>TP53/n</i> (%) 0.748 ⁸ Mutation 6 (13.3) 5 (11.1) 2 (5.4) 2 (5.4)	Absence	42 (93.3)	43 (95.6)		34 (91.9)	36 (97.3)			
Mutation $8 (18.2)$ $5 (11.1)$ $2 (5.4)$ $5 (13.5)$ Wildtype $36 (81.8)$ $40 (88.9)$ $35 (94.6)$ $32 (86.5)$ TET2/n (%)1.0008Mutation $6 (13.3)$ $6 (13.3)$ $2 (5.4)$ $2 (5.4)$ Wildtype $39 (86.7)$ $39 (86.7)$ $35 (94.6)$ $35 (94.6)$ TP53/n (%)0.7488Mutation $6 (13.3)$ $5 (11.1)$ $2 (5.4)$ Mutation $6 (13.3)$ $5 (11.1)$ $2 (5.4)$ $2 (5.4)$	NRAS/KRAS/n (%)			0.345§			0.430§		
Wildtype 36 (81.8) 40 (88.9) 35 (94.6) 32 (86.5) TET2/n (%) 1.0008 1.0008 1.0008 Mutation 6 (13.3) 6 (13.3) 2 (5.4) 2 (5.4) Wildtype 39 (86.7) 39 (86.7) 35 (94.6) 35 (94.6) TP53/n (%) 0.7488 Mutation 6 (13.3) 5 (11.1) 2 (5.4) 2 (5.4)	Mutation	8 (18.2)	5 (11.1)		2 (5.4)	5 (13.5)			
TET2/n (%) 1.0008 1.0008 Mutation 6 (13.3) 6 (13.3) 2 (5.4) 2 (5.4) Wildtype 39 (86.7) 39 (86.7) 35 (94.6) 35 (94.6) TP53/n (%) 0.7488 1.0008 Mutation 6 (13.3) 5 (11.1) 2 (5.4) 2 (5.4)	Wildtype	36 (81.8)	40 (88.9)		35 (94.6)	32 (86.5)			
Mutation 6 (13.3) 6 (13.3) 2 (5.4) 2 (5.4) Wildtype 39 (86.7) 39 (86.7) 35 (94.6) 35 (94.6) TP53/n (%) 0.748 ^s 1.000 ^s Mutation 6 (13.3) 5 (11.1) 2 (5.4) 2 (5.4)	TET2/n (%)			1.000§			1.000§		
Wildtype 39 (86.7) 39 (86.7) 35 (94.6) 35 (94.6) TP53/n (%) 0.748 [§] 1.000 [§] Mutation 6 (13.3) 5 (11.1) 2 (5.4) 2 (5.4)	Mutation	6 (13.3)	6 (13.3)		2 (5.4)	2 (5.4)			
TP53/n (%) 0.748 [§] 1.000 [§] Mutation 6 (13.3) 5 (11.1) 2 (5.4) 2 (5.4)	Wildtype	39 (86.7)	39 (86.7)		35 (94.6)	35 (94.6)			
Mutation 6 (13.3) 5 (11.1) 2 (5.4) 2 (5.4)	TP53/n (%)			0.748^{s}			1.000§		
	Mutation	6 (13.3)	5 (11.1)		2 (5.4)	2 (5.4)			

Characteristics	Chemotherapy group			Allo-HSCT group		
	High miR-98 (n = 45)	Low miR-98 (n = 45)	Р	High miR-98 (n = 37)	Low miR-98 (n = 37)	Р
Wildtype	39 (86.7)	40 (88.9)		35 (94.6)	35 (94.6)	
Relapse/n (%)			0.078§			1.000§
Yes	12 (26.7)	20 (44.4)		12 (32.4)	12 (32.4)	
No	33 (73.3)	25 (55.6)		25 (67.6)	25 (67.6)	

Abbreviations: WBC, white blood cell; BM, bone marrow; PB, peripheral blood; FAB, French American British. ** denotes Mann-Whitney U test; '\$' denotes chi-square test.



Figure 1. Kaplan-Meier curves of EFS and OS in chemotherapy group and allo-HSCT group. (A, B) In chemotherapy group, high miR-98 expressers had longer EFS and OS than low expressers. (C, D) EFS and OS were not significantly different between high miR-98 expression group and low expression group in allo-HSCT group.

Survival analysis of chemotherapy and allo-HSCT groups

Survival analyses were estimated using the Kaplan-Meier method. In chemotherapy group, high miR-98 expressers had a longer EFS (P = 0.003) and OS (P = 0.004; Figure 1A and 1B) compared with low expressers, but EFS and OS were not significantly different between high miR-98 expression group and low expression group in allo-HSCT group (Figure 1C and 1D).

Prognostic value of miR-98 expression

To assess the prognostic significance of clinical and molecular characteristics, we chose miR-98 expression levels (low vs. high), age (< 60 vs. \geq 60 years), WBC counts (< 20×10^9 /L vs. \geq 20×10^9 /L), *FLT3-ITD* (positive vs. negative) and *NPM1* (mutated vs. wild), *DNMT3A* (mutated vs. wild) to do survival analysis.

In the chemotherapy group, univariate analysis indicated that low miR-98 expression and age \geq 60 years were unfavorable for both EFS and OS (all *P* < 0.01). Multivariate analysis showed that low miR-98 expression and age \geq 60 years were independent risk factors for both EFS and OS (all *P* < 0.05). WBC counts and other genetic abnormalities (*FLT3-ITD*, *NPM1*, *DNMT3A*) had no significant effect on EFS and OS (Table 2).

In the allo-HSCT group, univariate and multivariate analyses all indicated that miR-98 had no association with EFS and OS. Other clinical and molecular parameters also had no impact on EFS and OS in this group (Table 3).

In all patients, multivariate analysis indicated that allo-HSCT and age < 60 years were independent favorable factors for both EFS and OS (all P < 0.05) (Table 4).

Variables	EFS		OS		
	HR (95%CI)	P-value	HR (95%CI)	P-value	
Univariate analyses					
MiR-98 (high vs. low)	0.516 (0.321-0.829)	0.006	0.522 (0.324-0.841)	0.008	
Age (< 60 vs. \geq 60 years)	3.588 (2.005-6.421)	0.000	3.423 (1.919-6.106)	0.000	
WBC (< $20 \text{ vs.} \ge 20 \times 10^9/\text{L}$)	1.037 (0.655-1.644)	0.876	1.068 (0.674-1.693)	0.779	
FLT3-ITD (positive vs. negative)	1.261 (0.703-2.260)	0.436	1.192 (0.665-2.136)	0.555	
NPM1 (mutated vs. wild type)	1.120 (0.687-1.827)	0.649	1.044 (0.640-1.704)	0.862	
DNMT3A (mutated vs. wild type)	1.407 (0.852-2.322)	0.182	1.432 (0.868-2.362)	0.160	
Multivariate analyses					
MiR-98 (high vs. low)	1.796 (1.041-3.100)	0.035	1.739 (1.005-3.009)	0.048	
Age (< 60 vs. \geq 60 years)	3.681 (2.036-6.657)	0.000	3.411 (1.889-6.158)	0.000	
WBC (< $20 \text{ vs.} \ge 20 \times 10^9 / \text{L}$)	1.190 (0.721-1.965)	0.496	1.160 (0.703-1.913)	0.562	
FLT3-ITD (positive vs. negative)	0.893 (0.491-1.626)	0.712	1.035 (0.565-1.895)	0.913	
NPM1 (mutated vs. wild type)	1.175 (0.647-2.133)	0.596	1.326 (0.726-2.420)	0.359	
DNMT3A (mutated vs. wild type)	0.747 (0.423-1.320)	0.316	0.692 (0.399-1.201)	0.191	

Abbreviations: EFS, event-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; WBC, white blood cell.

Ta	ble	3.	Uni	- and	multivar	riate an	alyses	for	EFS	and	OS	in a	llo-H	SCT	grou	р
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Variables	EFS		OS			
	HR (95%CI)	P-value	HR (95%CI)	<i>P</i> -value		
Univariate analyses						
MiR-98 (high vs. low)	1.273 (0.749-2.163)	0.372	1.143 (0.673-1.941)	0.620		
Age (< 60 vs. ≥ 60 years)	1.042 (0.581-1.868)	0.890	1.448 (0.807-2.599)	0.215		
WBC (< 20 vs. $\ge 20 \times 10^9 / L$)	0.754 (0.442-1.285)	0.299	0.985 (0.578-1.680)	0.956		
FLT3-ITD (positive vs. negative)	1.719 (0.915-3.229)	0.092	1.588 (0.848-2.972)	0.148		
NPM1 (mutated vs. wild type)	0.907 (0.494-1.666)	0.753	0.910 (0.495-1.671)	0.761		
DNMT3A (mutated vs. wild type)	1.184 (0.643-2.178)	0.588	1.320 (0.715-2.438)	0.374		
Multivariate analyses						
MiR-98 (high vs. low)	0.818 (0.437-1.533)	0.531	0.740 (0.392-1.400)	0.355		
Age (< 60 vs. \geq 60 years)	1.193 (0.637-2.232)	0.581	1.531 (0.820-2.860)	0.181		
WBC (< 20 vs. $\ge 20 \times 10^9 / L$)	1.372 (0.767-2.454)	0.286	1.075 (0.605-1.907)	0.806		
FLT3-ITD (positive vs. negative)	0.529 (0.260-1.075)	0.078	0.559 (0.274-1.139)	0.109		
NPM1 (mutated vs. wild type)	1.351 (0.630-2.896)	0.439	1.240 (0.579-2.654)	0.580		
DNMT3A (mutated vs. wild type)	0.785 (0.410-1.506)	0.467	0.646 (0.333-1.255)	0.197		

Abbreviations: EFS, event-free survival; OS, overall survival; Allo-HSCT, allogeneic hematopoietic stem cell transplantation; HR, hazard ratio; CI, confidence interval; WBC, white blood cell.

Table 4. Multivariate analyses for EFS and OS based on all patients

Variables	EFS		OS		
	HR (95%CI)	P-value	HR (95%CI)	P-value	
MiR-98 (high vs. low)	1.405 (0.945-2.089)	0.093	1.465 (0.979-2.192)	0.064	
Age (< 60 vs. \geq 60 years)	2.254 (1.543-3.293)	0.000	2.358 (0.820-2.860)	0.000	
WBC (< $20 \text{ vs.} \ge 20 \times 10^9/\text{L}$)	1.349 (0.927-1.963)	0.118	1.177 (0.811-1.709)	0.391	
FLT3-ITD (positive vs. negative)	0.781 (0.502-1.215)	0.273	0.886 (0.565-1.389)	0.597	
NPM1 (mutated v wild type)	1.240 (0.788-1.952)	0.352	1.327 (0.840-2.098)	0.226	
DNMT3A (mutated v wild type)	0.731 (0.484-1.103)	0.136	0.685 (0.455-1.031)	0.070	
Chemotherapy vs. allo-HSCT	1.459 (1.015-2.097)	0.041	1.765 (1.219-2.556)	0.003	

Abbreviations: EFS, event-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; WBC, white blood cell; Allo-HSCT, allogeneic hematopoietic stem cell transplantation.

We also divided all patients into two groups based on median expression level of miR-98. In the low miR-98 expressers, allo-HSCT treatment were associated with longer EFS and OS than chemotherapy-alone (P = 0.001, P < 0.001, respectively; Figure 2A and 2B), but EFS and OS were not significantly different in high miR-98 expressers (Figure 2C and 2D).

Associations between genome-wide miRNA and gene-expression profiles and miR-98 expression

To further assess the role of miR-98 in AML, we derived miR-98-associated miRNA and gene expression profiles by high throughput sequencing from TCGA data. First, we found 251 up-regulated and 26 down-regulated miRNAs that were 100

80

60

40

20

0

ò

p=0.001

30

60

Allo-HSCT(n=33)

Chemotherapy(n=49)

90

120

Α

Event-free survival(%)



60

90

120



ò

30

Figure 2. Kaplan-Meier curves of EFS and OS in high and low miR-98 expression groups. (A, B) In low expression group, patients treated with allo-HSCT had longer EFS and OS than those treated with chemotherapy-only. (C, D) No significant survival differences were found between chemotherapy group and allo-HSCT group in high miR-98 expressors.

significantly associated with miR-98 expression (P <0.05, fold change = 1.5, Figure 3A). Second, we identified 277 genes were positively correlated with miR-98 expression, and 256 genes were negatively correlated with miR-98 expression (P < 0.05, fold change = 1.5, Figure 3B). These genes were presented in the aberrant expression heat map (Figure 3C). Further gene ontology (GO) enrichment analysis indicated that the genes associated with miR-98 expression were mainly involved in "embryonic morphogenesis", "definitive skeletal system hemopoiesis", "thyroid gland development", "negative regulation of myeloid cell differentiation", "L1CAM interactions", "signaling pathways regulating pluripotency of stem cells", "drug catabolic process", "sensory perception of sound", and "response to inorganic substance" pathways. (Figure 3D).

Discussion

Our study found that high miR-98 expression was more likely to occur in younger and good-risk patients, and more *RUNX1-RUNX1T* fusion was seen in high miR-98 expression group, suggesting that high miR-98 expression tend to coincide with good-risk AML and may have similar prognostic value as *RUNX1-RUNX1T*. In the chemotherapy group, multivariate analysis had proved that low miR-98 expression and age \geq 60 were independent adverse factors. But in the allo-HSCT group, univariate and multivariate analysis all showed no effect of miR-98 expression on EFS and OS, and in the entire cohort, the low miR-98 expressors who underwent allo-HSCT had longer EFS and OS. In all patients, multivariate analysis indicated that allo-HSCT was independent favorable factor for both EFS and OS. Thus, we speculated that the unfavorable influence of low miR-98 expression might be overcome by allo-HSCT.

The mechanisms of miR-98 in anti-tumorigenesis have been investigated. MiR-98 could suppress breast cancer angiogenesis and invasion by repressing the expression of *ALK4* and *MMP11*^[25]. MiR-98 could also suppress the growth and metastasis of salivary adenoid cystic carcinomas by inhibiting the oncogene *NRAS* via the regulation of the *RAS/MAPK/ERK* and *PI3K/AKT* pathways ^[26] and suppress cell invasion and migration in glioma by directly targeting Pre-B Cell Leukemia Homeobox 3 ^[27]. It targeted *SALL4* to inhibit proliferation, migration, and invasion of hepatocellular carcinoma ^[28]. It inhibited melanoma metastasis via inhibiting IL-6 signaling pathway ^[22]. Mir-98 could negative regulate the expression of tumor suppressor gene FUS1b in lung cancers ^[29]. In



Figure 3. Genome-wide gene/microRNA expression profile and cell signaling pathways associated with miR-98 expression. (A) Volcano plot of differential microRNA expression. miR-98^{high} and miR-

leukemia, it was found that miR-98 upregulation chemotherapy-sensitivity could improve and decrease leukemia cell proliferation by inhibiting E2F1 expression ^[30]. In the present study, miR-98 is associated with "definitive hemopoiesis", "negative regulation of myeloid cell differentiation", "signaling pathways regulating pluripotency of stem cells", and they play an important role in hematopoiesis, which suggests that miR-98 may play a prognostic role in leukemia by interacting with genes involved in these functional pathways. The detailed mechanism of miR-98 in AML leukemogenesis, however, should require further study.

In summary, we found that high miR-98 expression was a good prognostic factor in AML patients who only received chemotherapy. Patients with low miR-98 expression may benefit from allo-HSCT.

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Competing Interests

The authors have declared that no competing interest exists.

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