High miR-93 Expression Predicts Good Prognosis in Acute Myeloid Leukemia

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Abstract

Background: Overexpression of microRNA-93 (miR-93) predicted worse outcome in non-small cell lung cancer (NSCLC) and gastric cancer patients, yet the prognostic role of miR-93 in AML is still unclear.

Methods: To further verify the prognostic significance of miR-93, the Cancer Genome Atlas database (TCGA) was screened and 161 AML patients with miR-93 expression information were included in our study.

Results: Compared with the patients who received chemotherapy alone with lower miR-93 expression, those with higher miR-93 expression had significantly longer event-free survival (EFS) and overall survival (OS) (all $P < 0.05$). Moreover, the expression levels of miR-93 was no association with either EFS or OS in patients undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT). Multivariate analysis confirmed that high miR-93 expression was an independent favorable factor for EFS and OS in AML patients only receiving chemotherapy (all $P < 0.05$).

Conclusion: our study proved that high miR-93 expression could predict favorable prognosis in AML, but its prognostic effect could be overcome by allo-HSCT.

Background

Acute myeloid leukemia (AML) is a highly aggressive malignancy arising from abnormal hematopoietic stem cell clones, which are characterized by arrested differentiation and unchecked proliferation [1]. The leukemic cells harbor various molecular biomarkers, such as genetic mutations and aberrant genetic expressions, that can be discovered and quantified by the second generation sequencing technology. Some of these markers are extremely helpful in predicting outcome, or can even be treatment targets [2]. For example, *DNMT3A* and *FLT3-ITD* mutations could predict poor outcome [3, 4], while the biallelic *CEBPA* (*biCEBPA*) mutation is a good prognostic marker in AML [5, 6].

microRNAs (MiRNAs) are endogenous non-coding RNAs produced by eukaryotes and are approximately 22-nt in length [7]. They are involved in many important physiological processes such as cell differentiation, proliferation, and apoptosis [8–10]. Abnormal expression of miRNAs plays an important role in the risk stratification and prognosis of AML [11, 12]. For instance, high miR-181a expression suggested favorable prognostic outcome in cytogenetically normal AML (CN-AML) [13]. High expression levels of miR-98 and miR-99, and low expression levels of miR-122 and miR-328 have been associated with adverse prognosis in AML [14–17].

MiR-93 is involved in the tumorigenesis and the evolution of drug resistance in various tumors. The proliferation and colony formation of human colon cancer stem cells were inhibited by miR-93 [18]. It could also promote glioblastoma cell growth and angiogenesis by regulating integrin-β8 [19]. In addition, miR-93 can enhance the resistance of ovarian cancer cells to antitumor drugs by targeting PTEN [20].

Former studies have shown that high miR-93 expression was associated with poor prognosis in non-small cell lung cancer (NSCLC) and gastric cancer [21, 22].

The prognostic significance of miR-93 in AML has been not reported. In this study, we intended to evaluate the effects of miR-93 on AML survival. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is an effective treatment for AML to reduce recurrence and the leukemia residual disease, and prolong the survival [23]. Herein, we also analyzed whether allo-HSCT could affect the outcome in patients with different expression levels of miR-93.

Materials And Methods

Patients

From The Cancer Genome Atlas (TCGA) database (https://cancergenome.nih.gov/), a total of 161 AML patients with miR-93 expression report were included in this study [24]. Ninety patients received chemotherapy alone, and 71 also underwent allo-HSCT. Clinical characteristics at diagnosis were collected, including peripheral white blood cell (WBC) counts, blast percentages in peripheral blood (PB) and bone marrow (BM), French-American-British (FAB) subtypes, cytogenetic risk group, and frequencies of common recurrent genetic mutations. Event-free survival (EFS) and overall survival (OS) were the primary endpoints of the study. EFS was defined as the time from diagnosis to removal from the study due to relapse, death or failure to achieve complete remission. OS was defined as the time from diagnosis to death from any cause or was censored at the last follow-up. Informed consents were obtained from all patients, and study protocol was approved by the Human Research Council of University of Washington.

Statistical analysis

The clinical and molecular characteristics of patients were summarized using descriptive statistics. Data sets were described with median and/or range. Numerical data was compared using the Mann-Whitney *U* test, and categorical data was compared using the Chi-Square test. Survival was estimated using the Kaplan-Meier method and the log-rank test. Multivariate Cox proportional hazard models were constructed for EFS and OS using a limited backward elimination procedure. The confidence interval was 95%. Spearman rank correlation was used to determine the associations between gene expression profile and miR-93 expression. Multiple testing errors were assessed by false discovery rate (FDR). Differential expressed genes were selected based on |logFC| >1 and adjust P value < 0.05. The genes of the heatmap were selected based on the |logFC| ≥1.2 of the differential genes in volcano plot. KEGG (Kyoto Encyclopedia of Genes and Genomes) enrichment analysis was conducted to assess the signaling pathways associated with differential expression genes of miR-93. A two-sided $P < 0.05$ was considered as the cut-off value. All statistical analyses were performed by R software 3.5.0, SPSS software 20.0 and the GraphPad Prism software 7.0.

Results

Prognostic value of miR-93 expression

To evaluate the prognostic value of miR-93 in AML, patients who received either the chemotherapy-only or the allo-HSCT were divided into high and low expression subgroups according to the median miR-93 expression levels of each group, respectively. In the chemotherapy-only group, the high miR-93 expression subgroup had longer EFS and OS ($P = 0.037$ and $P = 0.024$, Fig. 1A-B). MiR-93 had no impact on EFS and OS in the allo-HSCT group (Fig. 1C-D).

Association of miR-93 expression with clinical and molecular characteristics in the chemotherapy-only group

The clinical and molecular characteristics of the patients who received the chemotherapy-only were shown in Table 1. Median age was 66 (range, 22–88), with 61 cases older than 60. Fifty were men. The medians of WBC counts, BM blast, and PB blast percentages were 15.6×10^9/L, 72%, and 28.5%, respectively. FAB subtypes were mainly M1, M2, and M4 (72.2%). Forty-six patients had abnormal karyotypes. The proportion of good, intermediate, and poor cytogenetic risk patients were 14.8%, 62.5%, and 22.7%, respectively. *NPM1* had the highest mutation frequency (n = 29, 32.2%), followed by *DNMT3A* (n = 25, 27.8%), *FLT3-ITD* (n = 16, 17.8%), *IDH1/2* (n = 16, 17.8%), *NRAS/KRAS* (n = 13, 14.4%), *TP53* (n = 11, 12.2%), *TET2* (n = 12, 13.3%), and *RUNX1* (n = 8, 8.9%). Then all patients who underwent chemotherapy-only were divided into either miR-93^{high} group or the miR-93^{low} group based on miR-93 median expression levels. In miR-93^{high} group, there were fewer patients with complex karyotype, more patients with *RUNX1-RUNX1T1*, more with good cytogenetic risk and fewer poor-risk, less frequent *NPM1* and *TP53* mutations (all $P < 0.05$). No significant differences were identified in gender distribution, peripheral WBC count, BM blast and PB blast percentage, and the frequencies of other genetic mutations *(FLT3*, *DNMT3A*, *RUNX1*, *TET2*, *IDH1/IDH2*, *NRAS/KRAS*) between the two groups.

Table 1
Comparison of clinical and molecular characteristics in the chemotherapy-only group

Characteristics	Total	miR-93		*P*
		High (n = 45)	Low (n = 45)	
Age/years, median (range)	66 (22–88)	64 (22–83)	67 (31–88)	0.309*
Age group/n (%)				
≥60 years	61 (67.8)	28 (62.2)	33 (73.3)	0.259§
<60 years	29 (32.2)	17 (37.8)	12 (26.7)	
Gender/n (%)				0.671§
Male	50 (55.6)	26 (57.8)	24 (53.3)	
Female	40 (44.4)	19 (42.2)	21 (46.7)	
WBC/$\times 10^9$/L, median (range)	15.6 (0.7-298.4)	14.3 (1-114.5)	16 (0.7-298.4)	0.305*
BM blasts/%, median (range)	72 (30–99)	72 (30–95)	74 (32–99)	0.997*
PB blasts/%, median (range)	28.5 (0–98)	46 (0–97)	22 (0–98)	0.207*
FAB subtypes/n (%)				
M0	8 (8.9)	3 (6.7)	5 (11.1)	0.459§
M1	20 (22.2)	11 (24.4)	9 (20.0)	0.612§
M2	21 (23.3)	13 (28.9)	8 (17.8)	0.213§
M4	24 (26.7)	11 (24.4)	13 (28.9)	0.634§
M5	13 (14.4)	6 (13.3)	7 (15.6)	0.764§
M6	1 (1.1)	1 (2.2)	0 (0.0)	0.315§
M7	3 (3.3)	0 (0.0)	3 (6.7)	0.078§
Cytogenetics/n (%)				
Normal	44 (50.0)	20 (45.4)	24 (54.5)	0.394§
Complex	12 (13.6)	2 (4.5)	10 (22.7)	0.013§

Abbreviations: WBC, white blood cell; BM, bone marrow; PB, peripheral blood; FAB, French American British;

'*' denotes Mann-Whitney *U* test; '§' denotes chi-square test.

Characteristics	Total	miR-93		*P*
		High (n = 45)	Low (n = 45)	
inv(16)/CBFβ-MYH11	7 (8.0)	5 (11.4)	2 (4.5)	0.237§
t(8;21)/RUNX1-RUNX1T1	6 (6.8)	6 (13.6)	0 (0.0)	0.011§
11q23/MLL	3 (3.4)	2 (4.5)	1 (2.3)	0.557§
-7/7q-	3 (3.4)	0 (0.0)	3 (6.8)	0.078§
t(9;22)/BCR-ABL1	1 (1.1)	0 (0.0)	1 (2.3)	0.315§
Others	12 (13.6)	9 (20.5)	3 (6.8)	0.062§
Risk/n (%)				
Good	13 (14.8)	11 (25.0)	2 (4.5)	0.007§
Intermediate	55 (62.5)	27 (61.4)	28 (63.6)	0.826§
Poor	20 (22.7)	6 (13.6)	14 (31.8)	0.042§
FLT3-ITD/n (%)				0.098§
Positive	16 (17.8)	11 (24.4)	5 (11.1)	
Negative	74 (82.2)	34 (75.6)	40 (88.9)	
NPM1/n (%)				0.042§
Mutation	29 (32.2)	10 (22.2)	19 (42.2)	
Wild type	61 (67.8)	35 (77.8)	26 (57.8)	
DNMT3A/n (%)				0.239§
Mutation	25 (27.8)	10 (22.2)	15 (33.3)	
Wild type	65 (72.2)	35 (77.8)	30 (66.7)	
IDH1/*IDH2*/n (%)				0.098§
Mutation	16 (17.8)	11 (24.4)	5 (11.1)	
Wild type	74 (82.2)	34 (75.6)	40 (88.9)	

Abbreviations: WBC, white blood cell; BM, bone marrow; PB, peripheral blood; FAB, French American British;

'*' denotes Mann-Whitney *U* test; '§' denotes chi-square test.

Characteristics	Total	miR-93		*P*
		High (n = 45)	Low (n = 45)	
NRAS/KRAS/n (%)				0.134§
Mutation	13 (14.4)	4 (8.9)	9 (20.0)	
Wild type	77 (85.6)	41 (91.1)	36 (80.0)	
RUNX1/n (%)				1.000§
Mutation	8 (8.9)	4 (8.9)	4 (8.9)	
Wild type	82 (91.1)	41 (91.1)	41 (91.1)	
TET2/n (%)				1.000§
Mutation	12 (13.3)	6 (13.3)	6 (13.3)	
Wild type	78 (86.7)	39 (86.7)	39 (86.7)	
TP53/n (%)				0.004§
Mutation	11 (12.2)	1 (2.2)	10 (22.2)	
Wild type	79 (87.8)	44 (97.8)	35 (77.8)	
Abbreviations: WBC, white blood cell; BM, bone marrow; PB, peripheral blood; FAB, French American British;				
'*' denotes Mann-Whitney *U* test; '§' denotes chi-square test.				

In order to further evaluate the prognostic value of miR-93, we constructed the multivariate Cox proportional hazard models (Table 2). The variables included the expression levels of miR-93 (high vs. low), age (≥ 60 vs. <60 years), peripheral WBC count (≥ 15×10^9/L vs. <15×10^9/L), BM blasts (≥ 70% vs. <70%), PB blasts (≥ 70% vs. <70%), *FLT3-ITD* (positive vs. negative) and common AML mutations (*NPM1*, *DNMT3A*, *TET2*, *RUNX1* and *NRAS/KRAS*, mutated vs. wild type).

Table 2
Multivariate analysis of EFS and OS in the chemotherapy-only group

Variables	EFS		OS	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
miR-93 (high vs. Low)	0.487 (0.282–0.844)	0.010	0.450 (0.257–0.791)	0.005
Age (≥ 60 vs. <60 years)	4.987 (2.619–9.495)	0.000	4.051 (2.163–7.584)	0.000
WBC (≥ 15 vs. $<15 \times 10^9$/L)	0.971 (0.565–1.670)	0.916	1.018 (0.592–1.751)	0.949
BM blasts (≥ 70 vs. <70%)	1.848 (1.058–3.226)	0.031	1.942 (1.105–3.414)	0.021
PB blasts (≥ 70 vs. <70%)	3.247 (1.622–6.502)	0.001	2.459 (1.204–5.023)	0.014
FLT3-ITD (positive vs. negative)	1.386 (0.705–2.726)	0.344	1.484 (0.728–3.028)	0.278
NPM1 (mutated vs. wild)	0.548 (0.269–1.117)	0.098	0.419 (0.204–0.859)	0.018
DNMT3A (mutated vs. wild)	1.738 (0.981–3.080)	0.058	1.872 (1.065–3.289)	0.029
RUNX1 (mutated vs. wild)	1.273 (0.559–2.897)	0.566	1.431 (0.630–3.253)	0.392
TET2(mutated vs. wild)	0.701 (0.333–1.474)	0.349	0.564 (0.270–1.177)	0.127
NRAS/KRAS (mutated vs. wild)	0.675 (0.307–1.488)	0.330	0.847 (0.390–1.841)	0.675

Abbreviations: EFS, Event-free survival; OS, Overall survival; HR, hazard ratio; CI, confidence interval; WBC, white blood cell;

BM, bone marrow; PB, peripheral blood

Multivariate analysis reported that high miR-93 expression was an independent favorable prognostic factor for both EFS and OS (all $P < 0.05$). In addition, age ≥ 60 years, BM blasts ≥ 70% and PB blasts ≥ 70% were also independent risk factors for EFS and OS (all $P < 0.05$). *NPM1* mutation was an independent favorable factor for OS ($P = 0.018$), while *DNMT3A* mutation played an independent negative role for OS ($P = 0.029$).

Associations between genome-wide gene expression profile and miR-93 expression

To further assess the role of miR-93 in AML, the high-throughput sequencing information from TCGA database was used to summarize the miR-93-associated gene expression profiles. By using a conservative cutoff for significance ($P < 0.05$), 1479 genes were identified to be positively correlated with miR-93 expression, and 985 genes were negatively associated with the expression of miR-93 (Fig. 2A). Genome-wide expression profile analysis showed that genes positively related to miR-93 expression included tumor suppressors (*SDPR*, *EHD2*, *KIAA0125, ZFP36L1*, *LILRA3*, *ABI3*, *SERPINA1*, *C5aR1*, *FCN1*, *BASP1*, *FCER1G* and *HK3*). However, there was a negative correlation between the expression of miR-93 and FGR(a tumorigenesis promoter in multiple leukemia) (Fig. 2B). Furthermore, GO enrichment analysis

suggested that the genes related to miR-93 expression were mainly concentrated in “staphylococcus aureus infection”, “complement and coagulation cascades”, “pertussis”, “osteoclast differentiation”, “B cell receptor signaling pathway” and “phagosome” signaling pathways (Fig. 2C).

Discussion

In this retrospective study, we identified that high miR-93 expression definitely had a favorable effect on the survival of AML patients who only received chemotherapy, but not in those who underwent allo-HSCT, implicating that allo-HSCT may negate its prognostic impact.

Increasing number of studies have shown that miR-93 participated in various important cancer cell biological processes including proliferation, apoptosis, angiogenesis, and drug resistance. In most cancers, the role of miR-93 is oncogenic. Fang, et. al., reported that in human glioblastoma, miR-93 promoted tumor growth and angiogenesis by targeting integrin-β8 [19]. In bladder cancer, miR-93 targeted pigment epithelium-derived factor (PEDF), accelerating cell proliferation and invasion [25]. MiR-93 can also down-regulate the expression of Smad7 gene by regulating TGF- β1/Smad3 dependent fibrosis, thus enhancing the drug resistance of prolactinoma cells [26]. In high-risk HPV-positive cervical cancer, knockdown miR-93 may reactivate the potential anti-proliferation gene *BTG3*, thus inhibiting tumor progression [27]. High expression of miR-93 also has oncogenic properties in prostate cancer by interfering the cell cycle [28]. In AML, on the other hand, our study has pointed out that miR-93 may be an antioncogene. Although its overexpression coincided with other established favorable prognostic factors such as *CEBPA* double mutations, *NPM1* mutations and *RUNX1-RUNX1T1*, its prognostic effect was still independent. MiR-93 may therefore exert distinct functions in different tumors, depending on the cell of origin.

In addition, we verified that the increased expression of miR-93 was also an independent good prognostic factor in AML patients undergoing chemotherapy. GO analysis demonstrated that genes (*SDPR*, *EHD2*, *KIAA0125*, *ZFP36L1*, *LILRA3*, *ABI3*, *SERPINA1*, *C5aR1*, *FCN1*, *BASP1*, *FCER1G*, *HK3* and *FGR*) involved in “staphylococcus aureus infection”, “complement and coagulation cascades”, “pertussis”, “osteoclast differentiation”, “B cell receptor signaling pathway” and “phagosome” signaling pathways were significantly correlated with miR-93 expression. Former studies have shown that overexpression of *BASP1* is related to the inhibition of t(8;21) AML cells proliferation [29]. As a cytoprotective gene, the low expression of *HK3* impaired the neutrophil differentiation of APL cells and promoted cell death after anthracycline treatment [30], high expression of *KIAA0125* suppressing cell proliferation, migration, and invasion [31]. *FGR* was a tumor promoter which was associated with growth of primary AML cell [32]. Zhang X et al. identified that the activation of staphylococcus aureus infection signaling pathway can cause apoptosis multiple tumor cells [33]. In addition, the B-cell receptor signaling pathway has been proved to be a therapeutic target of CLL [34]. Hence, these results may elucidate the possible causes of miR-93 overexpression leading to favorable prognosis of AML by participating in the above pathways, and further research is needed to explore the exact role of miR-93 in leukemia inhibition.

Our results are consistent with previous studies that age ≥ 60 years had adverse effects on the survival of AML, which may be due to the higher mutation burden, poorer baseline performance status and more complications in this age group [35]. We also demonstrated that BM blasts ≥ 70% and PB blasts ≥ 70% were independent risk factors for EFS and OS, which is consistent with previous researches that abnormal proliferation of BM blasts and PB blasts have a significant negative impact on the prognosis of AML [36]. In our study, *NPM1* mutation was an independent favorable factor for OS, and *DNMT3A* mutation was an independent risk factor for OS. These findings are in line with former findings that *NPM1* mutation was related with good prognosis [37], while *DNMT3A* mutation had a connection with inferior DFS (Disease-free survival) and a trend toward shorter OS in CN-AML [38].

Conclusion

Our study reveals that high miR-93 expression is associated with good prognosis in AML, but its prognostic effects may be negated by allo-HSCT. Larger prospective researches are needed to further valid our findings. How miR-93 participates in the intricate web of AML leukemogenesis is also worth investigating.

Abbreviations

AML: acute myeloid leukemia; BM: bone marrow; PB: peripheral blood; DFS: Disease-free survival; CN-AML: cytogenetically normal AML; allo-HSCT: Allogeneic hematopoietic stem cell transplantation.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that there is no conflict of interest.

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Authors' contributions

YL wrote the paper. LF designed and revised the paper. ZHC and YFP drew the figures and tables. LZC and YFD performed the literature search. All authors read and approved the final manuscript.

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Figures

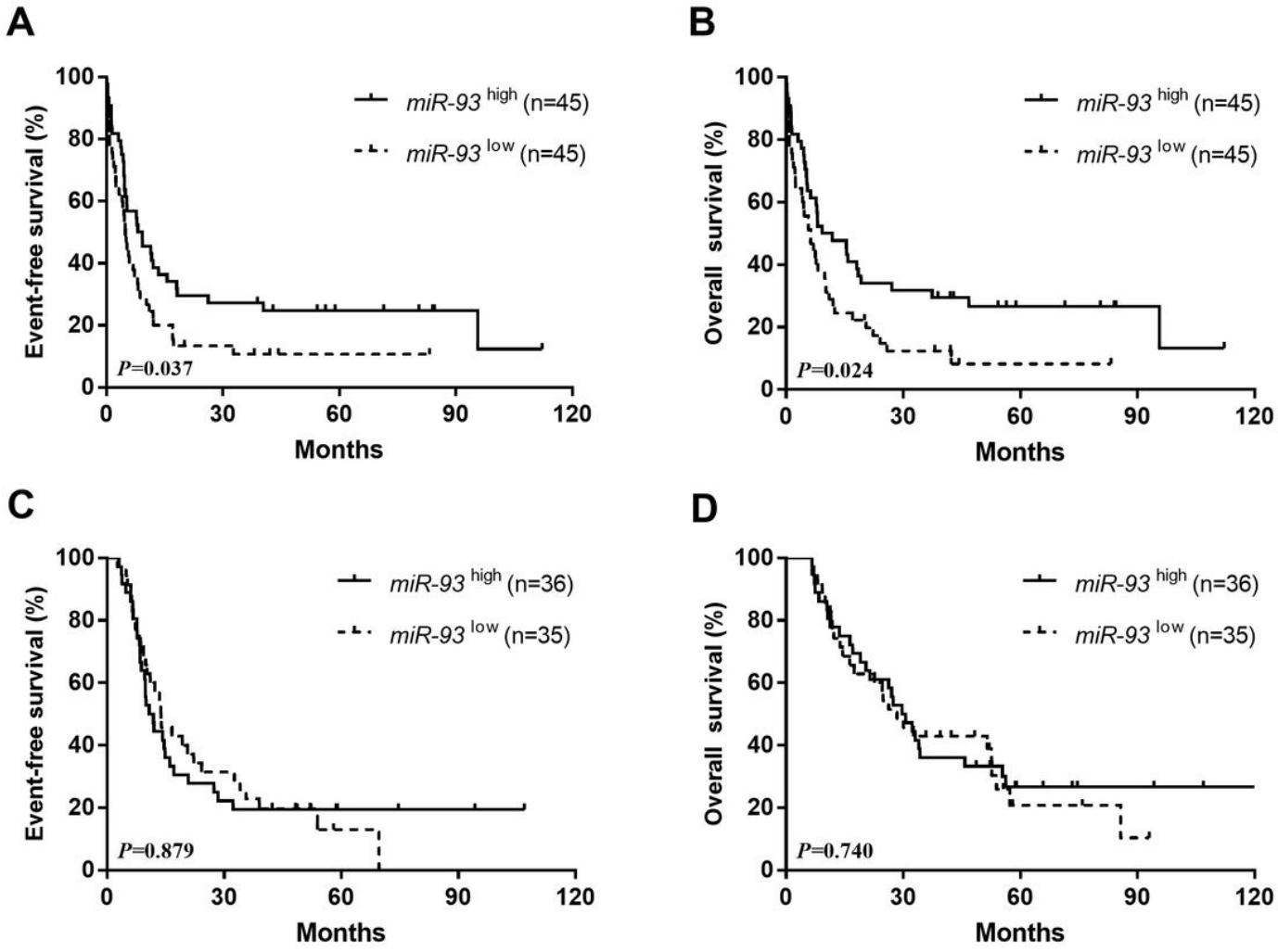

Figure 1

Kaplan-Meier curves of event-free survival (EFS) and overall survival (OS) in patients who received chemotherapy or allo-HSCT. A, B High miR-93 expressers had shorter EFS and OS than the low expressers in patients who received chemotherapy. C,D High expression of miR-93 had no impact on EFS and OS in the allo-HSCT group

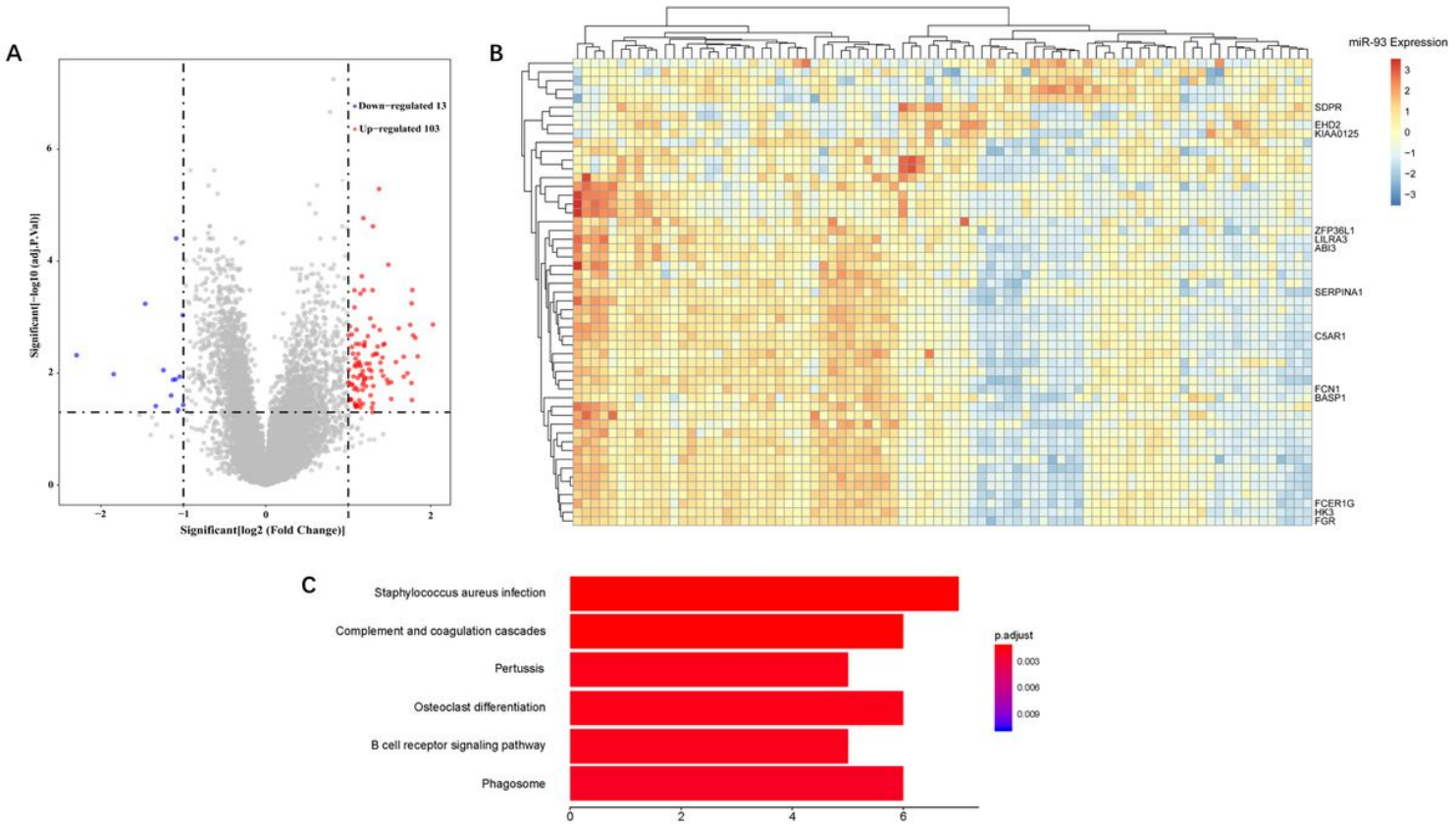

Figure 2

Genome-wide gene expression profile and cell signalling pathways associated with miR-93 expression. A Volcano plot of differential gene expression. Up-regulated and down-regulated genes were labelled with red and green dots, respectively. B Heatmap associated with miR-93 expression. C Signaling pathways associated with miR-93 expression.