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LETTER TO THE EDITOR

High *ETS2* expression predicts poor prognosis in acute myeloid leukemia patients undergoing allogeneic hematopoietic stem cell transplantation

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Dear Editor,

Acute myeloid leukemia (AML) is a common form of hematopoietic malignant disease with enormous cytogenetic and molecular heterogeneity. The biologic heterogeneity of AML is of great prognostic importance, which is well accepted [1]. Proper prognostic biomarkers can effectively guide therapeutic decision and improve a patient's quality of life and survival. With the advances of next-generation sequencing and big data analytics in molecular biology, more and more genetic mutations that have impacts on prognosis in AML patients have come into view. Genetic mutation is one of the most frequent molecular events contributed to the pathogenesis of AML [2]. So far, we have already known that *FLT3-ITD* and *DNMT3A* mutations usually bode a particularly poor prognosis [1, 3], while mutations in *NPM1* and double *CEBPA* are associated with favorable prognoses [4].

Not only the de novo mutational aberrations but also the change of gene expression level can affect the prognosis of AML. E26 transformation-specific sequence (ETS) was originally discovered as part of the gag-myb-ets transforming fusion protein of the avian erythroblastosis virus E26 [5]. Take *ERG*, a member of the Ets family located on chromosome 21 [6], as an example. *ERG* is required for the physiological hematopoietic stem cell (HSC) maintenance [7] and definitive hematopoiesis [8]. As one of the understood prognostic markers in AML, high expression of *ERG* is associated with poor patient outcomes. And our current study also showed that *ETS2*, another member of ETS family, is an inferior prognostic factor in AML and may guide treatment options towards allo-HSCT [9].

Allo-HSCT is an effective postremission therapy in AML, which can help patients with high-risk AML to get the most sustained disease-free remissions [10]. Minimal residual disease (MRD) status at the time of transplantation has been identified as the most important prognostic determinant of relapse in allo-HSCT [11]. Other prognostic factors include the time to transplant and cytogenetic risk group [11] [12].At the same time, however, a considerable portion of patients undergoing allo-HSCT meets a MRD-negative state relapse [13]. Thus, new prognostic implications like molecular abnormalities and genetic mutations in AML patients undergoing allo-HSCT have brought to our attention [14]. Though our previous study has clarified the prognostic significance of *ETS2* in AML, due to the effective anti-leukemic effect of allo-HSCT, whether the expression level of *ETS2* has prognostic significance in AML patients undergoing allo-HSCT is still unknown. In the study, we

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mainly discuss the prognostic value in AML patients undergoing allo-HSCT to assess the treatment effect.

Materials and methods

Patients

A total of 71 patients (30 females, 41 males) derived from The Cancer Genome Atlas (TCGA) (https://cancergenome.nih.gov/) database were rolled in the study. All of the 71 patients received allo-HSCT. Expression levels of *ETS2* as well as detailed clinical and molecular information of the patients were provided. Demographic information like age and gender was included. Genetic mutations were detected by next-generation sequencing. In the study, 71 patients were divided into two groups ($ETS2^{high}$ group and $ETS2^{low}$ group) based on the median level of *ETS2* expression. All these data were publicly available on the TCGA website.

The study was approved by the Human Research Ethics Committee of Washington University with written informed consent obtained from all the patients.

Statistical analysis

The software of SPSS version 20.0 and GraphPad Prism software version 6.0 were used for all the statistical analysis.

In the study, the demographics, clinical, and molecular information were described by descriptive statistics. Continuous data was presented in the form of median with range. The Mann-Whitney *U* test was used in comparison between two groups of continuous variables, and chi-square analysis was applied to evaluate the difference of categorical variables. The end points were event-free survival (EFS) and overall survival (OS). EFS was defined as the timespan from diagnosis to removal from the study, during which there are no objective signs of the absence of complete remission, recurrence, or death. OS was defined as the time from diagnosis to any cause of death. The EFS and OS were analyzed using the Kaplan–Meier method and the survival curves were plotted. The study used a Cox proportional hazard model to assess the influence of *ETS2* expression on prognosis. For all statistical analysis, a two-sided P value < 0.05 was considered as the cut-off value.

Availability of data and materials The datasets of this article were generated by TCGA.

Result

Demographic and prognostic factors of different *ETS2* expression levels

Among the study population, there was no difference between two groups in demographic information including age, age group, and gender. Between two groups, no significant differences were found in WBC count, bone marrow blasts, and peripheral blood blasts proportion. *ETS2* expression level had nothing to do with patients' FAB classification, karyotype, and risk distribution. In regard to common mutations in AML patients, no significant differences were revealed between two groups, including most conclusive prognostic factors like *FLT3-ITD*, *NPM1*, *DNMT3A*, and others mutations like *IDH1*, *IDH2*, *WT1*, *RUNX1*, *MLL-PTD*, *NRAS/KRAS*, *TET2*, *TP53*, *KIT*, *PTPN11*, and *PHF6*. Relapse rate showed no significance between $ETS2^{high}$ group and $ETS2^{low}$ group. As for HSCT types, no significant difference was found in type distribution between two group. The status of patients before transplant had no difference between ETS^{high} and ETS^{low} groups. However, there was a difference between two groups in the number of patients who underwent transplant in first complete remissiom (CR1, $P = 0.006$). We summarized the clinical and molecular characteristics and prognostic factors in Table 1.

$ETS2^{high}$ was associated with a poor prognosis in univariate and multivariate analysis

Using univariate analysis, we evaluated the prognostic significance of *ETS2* expression levels as well as clinical and molecular characteristics. Except for *ETS2* expression (high vs. low), age (< 60 vs. ≥ 60 years), WBC count ($< 30 \times 10^9$/L vs. $\geq 30 \times 10^9$/L), molecular risk, and common gene mutations (*FLT3-ITD*, *NPM1*, *DNMT3A*, *WT1*, *RUNX1*, *TP53*, *PHF6*, and *MLL-PTD*; mutated vs. wild) were involved in the analysis.

$ETS2^{high}$ patients had prominently shorter EFS (Table 2, $P = 0.016$) and OS (Table 2, $P = 0.006$) compared with $ETS2^{low}$ patients. Mutations in *PHF6* and *MLL-PTD* showed negative effects on both EFS ($P = 0.010$, 0.001) and OS ($P = 0.027$, 0.024). And mutations in *RUNX1* and *TP53* adversely affected OS ($P = 0.024$, 0.009), whether patients who received a transplant in CR1 affected EFS ($P = 0.010$).

Then we selected factors from univariate analysis based on above-mentioned statistical significance and frequency of mutations in AML patients (Table 3). After multivariate COX regression analyses, we found that $ETS2^{high}$ was associated with an adverse prognosis for unfavorable EFS ($P = 0.019$) and OS ($P = 0.015$), which was an independent prognostic

Table 1 Clinical and molecular characteristics of $ETS2^{high}$ and $ETS2^{low}$ patients

Characteristics	$ETS2^{high}$ ($n = 35$)	$ETS2^{low}$ ($n = 36$)	U/χ^2	P value
Age/years, median (range)	51(18–72)	50(22–69)	667.0*	0.670
Age group/*n* (%)			1.994§	0.188
< 60 years	23(67.5)	29(80.6)		
≥ 60 years	12(34.3)	7(19.4)		
Gender/*n* (%)			1.129§	0.341
Male	18(51.4)	23(63.9)		
Female	17(48.6)	13(36.1)		
WBC count/$\times 10^9$/L, median (range)	34.2(0.6–223.8)	22.5(1.2–202.7)	692.5*	0.472
BM blasts/%, median (range)	71(34–95)	70(30–100)	650.0*	0.230
PB blasts/%, median (range)	58(0–90)	41(0–96)	731.0*	0.164
FAB subtypes/*n* (%)			8.144§	0.420
M0	5(14.3)	4(11.1)	0.162§	0.688
M1	15(42.9)	8(22.2)	3.450§	0.063
M2	8(22.9)	10(27.8)	0.227§	0.634
M3	0(0.0)	1(2.8)	0.986§	0.321
M4	5(14.3)	8(22.2)	0.747§	0.387
M5	1(2.9)	3(8.3)	1.001§	0.317
M6	0(0.0)	1(2.8)	0.986§	0.321
M7	1(2.9)	0(0.0)	1.043§	0.307
Karyotype/*n* (%)			8.369§	0.497
Normal	17(48.6)	16(44.4)	0.122§	0.727
Complex	7(20.0)	4(11.1)	1.071§	0.343
8 Trisomy	3(8.6)	3(8.3)	0.001§	0.971
inv(16)/CBFβ-MYH11	2(5.7)	3(8.3)	0.186§	0.666
11q23/MLL	2(5.7)	1(2.8)	0.378§	0.539
-7/7q-	1(2.9)	2(5.6)	0.319§	0.572
t(15;17)/PML-RARA	0(0.0)	1(2.8)	0.986§	0.321
t(9;22)/BCR-ABL1	2(5.7)	0(0.0)	2.117§	0.146
t(8;21)/RUNX1-RUNX1T1	0(0.0)	1(2.8)	0.986§	0.321
Others	1(2.9)	5(13.9)	2.792§	0.095
Risk/*n* (%)			2.663§	0.446
Good	2(5.7)	5(13.9)	1.334§	0.248
Intermediate	20(57.1)	20(55.6)	0.018§	0.893
Poor	13(37.1)	10(27.8)	0.711§	0.399
FLT3-ITD			0.735§	0.391
Presence	12(34.3)	9(25.0)		
Absence	23(65.7)	27(75.0)		
NPM1			1.347§	0.246
Mutation	11(31.4)	7(19.4)		
Wild type	24(68.6)	29(80.6)		
CEBPA			0.535§	0.765
Single mutation	2(5.7)	3(8.3)		
Double mutation	1(2.9)	2(5.6)		
Wild type	32(91.4)	31(86.1)		
DNMT3A			0.537§	0.464
Mutation	8(22.9)	11(30.6)		
Wild type	27(77.1)	25(69.4)		
IDH1			1.996§	0.158
Mutation	7(20.0)	3(8.3)		
Wild type	28(80.0)	33(91.7)		
IDH2			0.002§	0.966
Mutation	4(11.4)	4(11.1)		
Wild type	31(88.6)	32(88.9)		
WT1			0.002§	0.966
Mutation	4(11.4)	4(11.1)		
Wild type	31(88.6)	32(88.9)		
RUNX1			0.002§	0.966
Mutation	4(11.4)	4(11.1)		
Wild type	31(88.6)	32(88.9)		
MLL-PTD			1.120§	0.290
Presence	3(8.6)	1(2.8)		
Absence	32(91.4)	35(97.2)		
NRAS/KRAS			0.129§	0.720
Mutation	3(8.6)	4(11.1)		
Wild type	32(91.4)	32(88.9)		
TET2			1.001§	0.317
Mutation	1(2.9)	3(8.3)		
Wild type	34(97.1)	33(91.7)		
TP53			0.001§	0.977

Table 1 (continued)

Characteristics	ETS2^{high} ($n = 35$)	ETS2^{low} ($n = 36$)	U/χ^2	P value
Mutation	2(5.7)	2(5.6)		
Wild type	33(94.3)	34(94.4)		
KIT			0.378§	0.539
Mutation	2(5.7)	1(2.8)		
Wild type	33(94.3)	35(97.2)		
PTPN11			0.002§	0.966
Mutation	4(11.4)	4(11.1)		
Wild type	31(88.6)	32(88.9)		
PHF6			0.001§	0.977
Mutation	2(5.7)	2(5.6)		
Wild type	33(94.3)	34(94.4)		
Relapse			0.461§	0.497
Yes	25(71.4)	23(63.9)		
No	10(28.6)	13(36.1)		
HSCT			3.828§	0.148
Haplo	0(0.0)	2(5.6)	2.001§	0.157
Sib allo	18(51.4)	12(33.3)	2.382§	0.123
MUD	17(48.6)	22(61.1)	1.127§	0.288
Transplant status/*n* (%)			2.124§	0.173
Active disease	11(31.4)	6(16.7)		
CR	24(68.6)	30(83.3)		
Transplant in CR1/*n* (%)			7.491§	0.006
Yes	14(40.0)	26(72.2)		
No	21(60.0)	10(27.8)		

WBC white blood cell, *BM* bone marrow, *PB* peripheral blood, *FAB* French American British, *HSCT*, hematopoietic stem cell transplantation, *Haplo* haploidentical, *Allo* allogeneic, *MUD* matched unrelated donor, *CR* complete remission

*Mann-Whitney *U* test

§Chi-square test

factor. Meanwhile, *PHF6* mutation contributed to poor EFS ($P = 0.023$), while *TP53* contributed to poor OS ($P = 0.015$). Other factors showed no significance on prognosis.

The survival curves further proved the poor prognostic effect of *ETS2* expression

Plotted by Kaplan–Meier method (Fig. 1), the survival curves proved the result that *ETS2*^{high} negatively correlated with EFS ($P = 0.014$) and OS ($P = 0.004$).

Discussion

Our study showed that high expression of *ETS2* can shorten EFS and OS in AML patients undergoing allo-HSCT. Combined with foregoing research, the result indicated that in AML *ETS2* was a powerful prognostic factor, whose unfavorable effect could not be overridden by allo-HSCT.

While plenty of prognostic factors in AML are relatively understood, indicators influencing the outcome after allo-HSCT need further investigation. Genetic mutations have close

Table 2 Univariate analysis for EFS and OS

Variables	EFS		OS	
	HR (95%CI)	P value	HR (95%CI)	P value
ETS2 (high vs. low)	1.892(1.129–3.169)	0.016	2.197(1.259–3.831)	0.006
Age (≥ 60 vs. <60 years)	0.825(0.458–1.485)	0.522	1.406(0.769–2.571)	0.268
WBC (≥ 30 vs. < 30×10^9/L)	1.614(0.965–2.699)	0.068	0.986(0.571–1.702)	0.959
Risk (poor vs. non-poor)	0.966(0.554–1.685)	0.904	1.283(0.717–2.294)	0.401
FLT3-ITD (negative vs. positive)	0.752(0.431–1.314)	0.317	0.083(0.440–1.467)	0.476
NPM1 (wild vs. mutated)	1.215(0.666–2.216)	0.525	1.243(0.651–2.372)	0.510
DNMT3A (wild vs. mutated)	1.038(0.576–1.870)	0.901	0.861(0.464–1.596)	0.634
WT1 (wild vs. mutated)	0.503(0.225–1.121)	0.093	0.630(0.281–1.410)	0.261
RUNX1 (wild vs. mutated)	0.708(0.334–1.498)	0.366	0.410(0.190–0.887)	0.024
TP53 (wild vs. mutated)	0.594(0.212–1.664)	0.322	0.234(0.079–0.696)	0.009
PHF6 (wild vs. mutated)	0.235(0.078–0.709)	0.010	0.310(0.109–0.878)	0.027
MLL-PTD (negative vs. positive)	0.151(0.051–0.450)	0.001	0.302(0.107–0.854)	0.024
Transplant in CR1 (yes vs. no)	0.504(0.299–0.850)	0.010	0.901(0.522–1.555)	0.708

EFS event-free survival, *OS* overall survival, *WBC* white blood cell, *CR* complete remission, *HR* hazard ratio, *CI* confidence interval

Table 3 Multivariate analysis for EFS and OS

Variables	EFS		OS	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
ETS2 (high vs. low)	2.186(1.135–4.210)	0.019	2.521(1.197–5.307)	0.015
Age (≥ 60 vs. <60 years)	0.833(0.398–1.745)	0.628	0.952(0.447–2.026)	0.897
WBC (≥ 30 vs. < 30×10^9/L)	1.624(0.863–3.056)	0.133	0.837(0.415–1.681)	0.621
Risk (poor vs. non-poor)	0.843(0.416–1.708)	0.635	1.105(0.502–2.432)	0.804
FLT3-ITD (negative vs. positive)	0.550(0.269–1.126)	0.102	0.438(0.195–0.986)	0.046
NPM1 (wild vs. mutated)	2.172(0.927–5.092)	0.074	2.008(0.760–5.309)	0.160
DNMT3A (wild vs. mutated)	0.750(0.378–1.487)	0.410	0.604(0.280–1.301)	0.198
WT1 (wild vs. mutated)	0.615(0.208–1.820)	0.380	0.963(0.298–3.106)	0.949
RUNX1 (wild vs. mutated)	1.057(0.436–2.562)	0.903	0.508(0.209–3.106)	0.135
TP53 (wild vs. mutated)	0.310(0.086–1.113)	0.072	0.187(0.048–1.243)	0.015
PHF6 (wild vs. mutated)	0.218(0.059–0.811)	0.023	0.307(0.076–1.243)	0.098
MLL-PTD (negative vs. positive)	0.258(0.063–1.052)	0.059	0.550(0.141–2.151)	0.390
Transplant in CR1 (yes vs. no)	1.806(0.909–3.589)	0.092	1.074(0.481–2.400)	0.861

EFS event-free survival, *OS* overall survival, *CR* complete remission, *HR* hazard ratio, *CI* confidence interval

relations with the prognosis of AML patients undergoing allo-HSCT. Among the common pathogenic mutations, *FLT3-ITD*, *TP53*, and *WT1* mutations were associated with higher risk of relapse after allo-HSCT [14]. *FLT3-ITD* with *DNMT3A* R882 double mutation is an independent unfavorable factor after allo-HSCT [3]. And Schmid et al. said that in AML patients undergoing allo-HSCT, *FLT3-ITD* mutation was identified as a decisive factor for outcome rather than other mutations [15]. In our multivariate analysis, high expression of *ETS2* can shorten both EFS and OS, which implies that *ETS2* is more influential than classical mutations like *FLT3-ITD*, *NPM1*, and *DNMT3A* in predicting the outcome in AML patients after allo-HSCT. Other mutations like *TP53*and *PHF6* can only affect the length of EFS or OS. Over the years, allo-HSCT was a restriction in CR1 for the fear of early death [16], while in our study, those who received transplant in CR1 or did not had no influenced on either EFS or OS in multivariate analysis. Hence, we may deduce that *ETS2* is a better prognostic biomarker than traditional biomarker for AML patients undergoing allo-HSCT.

With a characteristic winged helix-turn-helix DNA binding domain [17], the transcription factor *ETS2* can bind to a conserved GGAA/T core sequences within promoter regions of target genes [18]. As one of the major downstream effectors of oncogenic Ras, *ETS2* has close relationships with various cellular physiological activities. Phosphorylated by ERK1/2 at Thr72 and Ser75, *ETS2* has enhanced association with transcriptional co-activators p300 and CREB binding protein (CBP), promoting the initiation of transcription of target genes [19]. Recent research has revealed that the transcription factors *ERG* and *ETS2* can be involved in leukemogenesis [20]. And overexpression of *ETS2* with loss of TP53 might result in aberrance of the apoptotic pathways in hematopoietic system [21]. Our recent research has demonstrated that high *ETS2* level is an adverse prognostic biomarker for AML and may guide treatment choices towards allo-HSCT [9]. And the

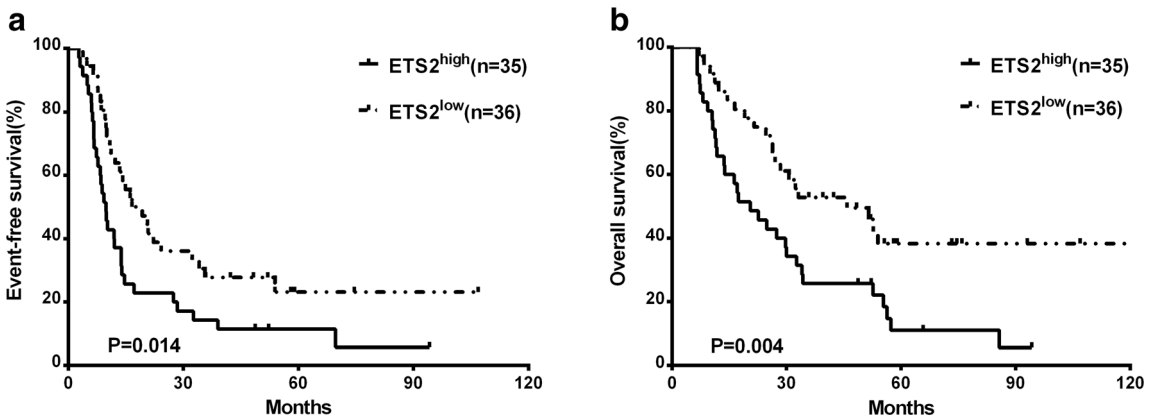

Fig. 1 Kaplan–Meier curves of EFS and OS. (**a**, **b**) Patients in *ETS2*^{high} group have shorter EFS and OS than those in *ETS2*^{low} group

results mentioned before further confirmed the adverse effect of *ETS2*. Although according to our preliminary study, allo-HSCT is more effective than chemotherapy and can prolong survival for $ETS2^{high}$ patients, *ETS2* was associated with poor prognosis even for patients undergoing allo-HSCT. However, due to the limit of cases, the relationship between *ETS2* and other biomarkers cannot get an accurate analysis. Moreover, as one of the important target genes for RAS/MAPK pathway and phosphatidylinositol 3-kinase/Akt pathways, the prognostic significance of *ETS2* may inspire us to investigate the *ETS2* target therapy. And the detailed mechanism of *ETS2* in leukemogenesis needs further research.

Conclusion

In summary, high *ETS2* expression predicts poor prognosis not only in AML but also in AML patients undergoing allo-HSCT and can be regarded as a new biomarker for AML.

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Authors' contributions Jinlong Shi, Lin Fu, and Xiaoyan Ke designed the study; Gaoqi Zhang wrote the manuscript; Xinrui Yang, Xinpei Zhang, Jilei Zhang, Siyuan Yang, and Jing Wang performed statistical analyses and analyzed the data. Jinlong Shi, Xiaoyan Ke, and Lin Fu coordinated the study over the entire time. All authors approved the final manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Consent for publication Not applicable.

Ethics approval and consent to participate The study was approved by the Human Research Ethics Committee of Washington University with written informed consent obtained from all the patients.

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