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RESEARCH PAPER

High *EGFL7* expression may predict poor prognosis in acute myeloid leukemia patients undergoing allogeneic hematopoietic stem cell transplantation

Zhiheng Cheng [a,b,c,d], Yifeng Dai [e], Yifan Pang[f], Yang Jiao [g], Yan Liu[d], Longzhen Cui[d], Tingting Qian[c], Liang Quan[c], Wei Cui[h], Yue Pan[h], Xu Ye[a], Jinlong Shi[i], and Lin Fu [a,c,j]

[a]Department of Hematology, The Second Affiliated Hospital of Guangzhou Medical University, Guangzhou, China; [b]Department of Pathology and Medical Biology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands; [c]Translational Medicine Center, The Second Affiliated Hospital of Guangzhou Medical University, Guangzhou, China; [d]Translational Medicine Center, Huaihe Hospital of Henan University, Kaifeng, China; [e]Immunoendocrinology, Division of Medical Biology, Department of Pathology and Medical Biology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands; [f]Department of Medicine, William Beaumont Hospital, Royal Oak, MI, USA; [g]Life Sciences Institute and Innovation Center for Cell Signaling Network, Zhejiang University, Hangzhou, China; [h]Department of Clinical Laboratory, Beijing Haidian Hospital, Beijing Haidian Section of Peking University Third Hospital, Beijing, China; [i]Department of Biomedical Engineering, Chinese PLA General Hospital, Beijing, China; [j]Department of Hematology, Huaihe Hospital of Henan University, Kaifeng, China

ABSTRACT

Epithelial growth factor-like 7 (EGFL7) is a secretory protein with a well-characterized role in angiogenesis and the oncogenesis of certain solid tumors. Overexpression of *EGFL7* is associated with adverse prognosis in patients with cytogenetically normal acute myeloid leukemia (CN-AML). However, whether this association persists after allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains unclear. To further clarify the prognostic role of *EGFL7*, seventy-one AML patients with *EGFL7* expression data who underwent allo-HSCT from The Cancer Genome Atlas database were included and divided into either $EGFL7^{high}$ or $EGFL7^{low}$ group based on the median *EGFL7* expression level. Two groups had similar clinical and molecular characteristics except that the $EGFL7^{high}$ group had less frequent *NPM1* mutations ($P = .001$). Kaplan-Meier survival curves showed that high *EGFL7* expressers had shorter OS than the low expressers ($P = .040$). Univariate analysis showed that high *EGFL7* expression, *MLL-PTD, RUNX1* and *TP53* mutations were associated with short OS (all $P < .05$). Multivariate analysis indicated that high *EGFL7* expression, *FLT3-ITD, RUNX1* and *TP53* mutations were independent risk factors for OS (all $P < .05$). Collectively, our study suggested that *EGFL7*, like the other widely-used risk stratification factors, could serve as a prognostic tool and therapeutic target in AML, even after allo-HCST.

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Introduction

The clinical and genetic heterogeneity of acute myeloid leukemia (AML) has made pre-treatment genetic mutation and expression profiling a pre-requisite for individualized prognostication and treatment.[1,2] For example, *DNMT3A* and *TP53* mutations are poor-prognostic factors,[3,4] while *NPM1* mutation is associated with favorable prognosis.[5] With the advances in molecular diagnostics, not only the mutations, but also the abnormal expression of certain genes can be utilized for refined risk stratification of AML. Over-expressions of *DOK4/5, PDK2/3, FHL2*, and *iASPP* are associated with poor prognosis, whereas overexpression of *DOK7* correlates with good prognosis.[6–8] Due to the complexity of AML leukemogenesis and treatment, it is in dire need to find more and better risk stratification markers in the foreseeable future.

Epithelial growth factor-like 7 (EGFL7) is a secretory endothelial cell protein that contains two epidermal growth factor-like domains and plays an important role in regulating vasculogenesis.[9] A previous study showed that *EGFL7* was highly expressed in human epithelial tumor tissues, including lung cancer, hepatocellular carcinoma, gastric cancer, esophageal cancer, and renal cancer.[10] Some studies have indicated that high *EGFL7* expression was associated with poor prognosis and advanced stages in multiple types of human cancer, including epithelial ovarian cancer, pancreatic cancer, and gastric cancer.[11–13] Another recent study demonstrated that high expression of *EGFL7* was correlated with lower complete remission (CR) rates, shorter event-free survival (EFS) and overall survival (OS) in patients with cytogenetically normal AML (CN-AML).[14]

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) significantly reduces leukemia residual disease and has conferred cure on many AML patients.[15] However, it remains unclear whether the prognostic effect of *EGFL7* will persist after allo-HSCT. We aim to answer this question by studying whether high *EGFL7* expression predicts poor prognosis in AML patients who have undergone allo-HSCT.

Patients and methods

Patients

From The Cancer Genome Atlas (TCGA) database (https://cancergenome.nih.gov/), a total of seventy-one AML patients

CONTACT Lin Fu fulin022@126.com Department of Hematology, The Second Affiliated Hospital of Guangzhou Medical University, Guangzhou 510260, China

who underwent allo-HSCT and had *EGFL7* expression data were included in this study.[16] All patients were between ages 18 and 72. Clinical characteristics at diagnosis were available in the database, including peripheral blood (PB) white blood cell count (WBC), PB and bone marrow (BM) blast percentages, French-American-British (FAB) subtypes, and the frequencies of other genetic abnormalities. Overall survival (OS) was the primary endpoint of this study. OS was defined as the time from diagnosis to death of any cause, or was censored at the last follow-up. All patients provided informed consent, and the study protocol was approved by the Washington University Human Studies Committee.

Statistical analysis

Descriptive statistics were used to summarize the clinical and molecular characteristics of the patients. Data sets were described by median and/or range. As the numerical data were not normally distributed, we used the Wilcoxon-Mann-Whitney test to compare the two groups. Categorical data were compared using the chi-square test. Survival was estimated using the Kaplan-Meier methods and log-rank test. Univariate and multivariate Cox proportional hazard models were constructed for OS, using a limited backward elimination procedure. A two-tailed $P< .05$ was considered statistically significant. All statistical analyses were performed by SPSS software 25.0 and GraphPad Prism software 7.0.

Results

Differences in the clinical and molecular characteristics between the *EGFL7*^{high} and *EGFL7*^{low} groups

All patients were divided into two groups based on the median *EGFL7* expression level. Comparison of the two groups' clinical and molecular characteristics were showed in Table 1. *EGFL7*^{high} group had less frequent *NPM1* mutations ($P= .001$). No significant differences were found in age, gender distribution, WBC count, BM blasts, PB blasts, FAB subtypes, karyotype, and risk-group distribution. The two groups had similar mutation frequencies in *FLT3-ITD, DNMT3A, IDH1/IDH2, RUNX1, NRAS/KRAS, TET2, TP53*, and *MLL-PTD*. Relapse rate and HSCT donor type were similar in the two groups (all $P> .05$).

Prognostic value of EGFL7 expression

Kaplan-Meier analysis demonstrated that high *EGFL7* expressers had shorter OS than the low expressers ($P= .040$, Figure 1). To evaluate the prognostic significance of *EGFL7* expression level and other clinical or molecular variables, univariate and multivariate Cox proportional hazard models were constructed. The variables included expression levels of *EGFL7* (high vs. low), age (≥60 vs. <60 years), WBC count (≥15 × 10^9/L vs. <15 × 10^9/L), BM blasts (≥70% vs. <70%), PB blasts (≥20% vs. <20%), *FLT3-ITD* (positive vs. negative), *MLL-PTD* (positive vs. negative), and other common AML mutations (*NPM1, DNMT3A, RUNX1*, and *TP53*; mutated vs. wild). Results were shown in Tables 2 and 3.

Table 1. Clinical and molecular characteristics of the patients.

Characteristics	*EGFL7*^{high} (n = 35)	*EGFL7*^{low} (n = 36)	*P*
Age/years, median (range)	54 (22–72)	48 (18–63)	.102*
Age group/n (%)			.381§
<60 years	24 (68.6)	28 (77.8)	
≥60 years	11 (31.4)	8 (22.2)	
Gender/n (%)			.705§
Male	21 (60.0)	20 (55.6)	
Female	14 (40.0)	16 (44.4)	
WBC/×10^9/L, median (range)	29.4 (0.6–223.8)	29.6 (0.8–202.7)	.505*
BM blast/%, median (range)	67 (30–99)	78 (34–100)	.066*
PB blast/%, median (range)	49 (0–94)	48 (0–96)	.729*
FAB subtypes/n (%)			
M0	5 (14.3)	4 (11.1)	.735§
M1	13 (37.1)	10 (27.8)	.399§
M2	11 (31.4)	7 (19.4)	.246§
M3	0 (0.0)	1 (2.8)	1.000§
M4	4 (11.4)	9 (25.0)	.139§
M5	0 (0.0)	4 (11.1)	.115§
M6	1 (2.9)	0 (0.0)	.493§
M7	1 (2.9)	1 (2.8)	1.000§
Cytogenetics/n (%)			
Normal	14 (40.0)	19 (52.8)	.280§
Complex karyotype	5 (14.3)	6 (16.7)	.782§
8 Trisomy	4 (11.4)	2 (5.6)	.429§
inv(16)/CBFβ-MYH11	4 (11.4)	1 (2.8)	.199§
11q23/MLL	0 (0.0)	3 (8.3)	.239§
−7/7q-	3 (8.6)	0 (0.0)	.115§
t(15;17)/PML-RARA	0 (0.0)	1 (2.8)	1.000§
t(9;22)/BCR-ABL1	2 (5.7)	0 (0.0)	.239§
t(8;21)/RUNX1-RUNX1T1	1 (2.9)	0 (0.0)	.493§
Others	2 (5.7)	4 (11.1)	.674§
Risk/n (%)			
Good	5 (14.7)	2 (5.6)	.253§
Intermediate	16 (47.1)	24 (60.0)	.098§
Poor	13 (38.2)	10 (27.8)	.352§
FLT3-ITD/n (%)			.832§
Positive	8 (22.9)	9 (25.0)	
Negative	27 (77.1)	27 (75.0)	
NPM1/n (%)			.001§
Mutation	3 (8.6)	15 (41.7)	
Wild type	32 (91.4)	21 (58.3)	
DNMT3A/n (%)			.832§
Mutation	8 (22.9)	9 (25.0)	
Wild type	27 (77.1)	27 (75.0)	
IDH1/IDH2/n (%)			.368§
Mutation	10 (28.6)	7 (19.4)	
Wild type	25 (71.4)	29 (80.6)	
RUNX1/n (%)			.710§
Mutation	3 (8.6)	5 (13.9)	
Wild type	32 (91.4)	31 (86.1)	
NRAS/KRAS/n (%)			.710§
Mutation	4 (11.4)	3 (8.3)	
Wild type	31 (88.6)	33 (91.7)	
TET2/n (%)			.614§
Mutation	1 (2.9)	3 (8.3)	
Wild type	34 (97.1)	33 (91.7)	
TP53/n (%)			1.000§
Mutation	2 (5.7)	2 (5.6)	
Wild type	33 (94.3)	34 (94.4)	
MLL-PTD/n (%)			1.000§
Positive	2 (5.7)	2 (5.6)	
Negative	33 (94.3)	34 (94.4)	
Relapse/n (%)			.932§
Yes	23 (65.7)	24 (66.7)	
No	12 (34.3)	12 (33.3)	
HSCT			.903§
Haplo	1 (2.9)	1 (2.8)	
Sib allo	14 (40.0)	16 (44.4)	
MUD	20 (57.1)	19 (52.8)	

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

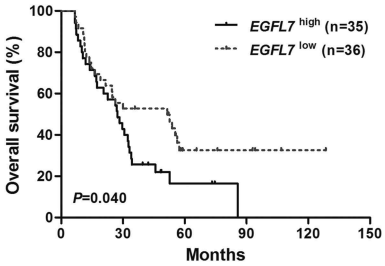

Figure 1. Kaplan-Meier curves of overall survival (OS) in the patients. Patients with high *EGFL7* expression had shorter OS than those with low expression.

Table 2. Univariate analysis of OS in the patients.

	OS	
Variables	HR (95%CI)	*P*-value
EGFL7 (high vs. Low)	1.789 (1.020–3.137)	.042
Age (≥60 vs. <60 years)	1.406 (0.769–2.571)	.268
WBC (≥15 vs. <15 × 10^9/L)	1.161 (0.665–2.028)	.600
BM blasts (≥70 vs. <70%)	0.840 (0.487–1.449)	.530
PB blasts (≥20 vs. <20%)	1.121 (0.607–2.071)	.716
FLT3-ITD (positive vs. negative)	1.666 (0.884–3.139)	.114
NPM1 (mutated vs. wild)	0.805 (0.422–1.536)	.510
DNMT3A (mutated vs. wild)	1.259 (0.668–2.374)	.477
RUNX1 (mutated vs. wild)	2.437 (1.127–5.270)	.024
TP53 (mutated vs. wild)	4.270 (1.437–12.688)	.009
MLL-PTD (positive vs. negative)	3.307 (1.171–9.334)	.024

Abbreviations: OS, Overall survival; HR, hazard ratio; CI, confidence interval; WBC, white blood cell; BM, bone marrow; PB, peripheral blood.

Table 3. Multivariate analysis of OS in the patients.

	OS	
Variables	HR (95%CI)	*P*-value
EGFL7 (high vs. Low)	2.307 (1.151–4.625)	.019
Age (≥60 vs. <60 years)	1.229 (0.614–2.459)	.560
WBC (≥15 vs. <15 × 10^9/L)	1.325 (0.674–2.602)	.415
BM blasts (≥70 vs. <70%)	0.833 (0.419–1.659)	.604
PB blasts (≥20 vs. <20%)	1.589 (0.753–3.354)	.224
FLT3-ITD (positive vs. negative)	2.406 (1.086–5.329)	.031
NPM1 (mutated vs. wild)	1.388 (0.562–3.430)	.477
DNMT3A (mutated vs. wild)	1.158 (0.562–2.383)	.691
RUNX1 (mutated vs. wild)	3.165 (1.332–7.521)	.009
TP53 (mutated vs. wild)	12.175 (3.161–46.895)	.000
MLL-PTD (positive vs. negative)	2.425 (0.776–7.577)	.128

Abbreviations: OS, Overall survival; HR, hazard ratio; CI, confidence interval; WBC, white blood cell; BM, bone marrow; PB, peripheral blood.

Univariate analysis showed that high *EGFL7* expression was associated with short OS (*P*= .042). *RUNX1* mutations, *TP53* mutations, and *MLL-PTD* were unfavorable for OS as well (*P*= .024, *P*= .009, *P*= .024, respectively). Multivariate analysis showed that high *EGFL7* expression was an independent risk factor for OS (*P*= .019), as well as *FLT3-ITD*, mutations in *RUNX1* and *TP53* (*P*= .031, *P*= .009, *P*< .001, respectively).

Discussion

Our findings suggested that high *EGFL7* expression was an independent risk factor for OS in AML patients who had undergone allo-HSCT, which not only concurred with the previous finding that high *EGFL7* expression was associated with worse outcome in CN-AML,[14] but also indicated that *EGFL7* could be a prognostic indicator unaffected by treatment.

The outcome of allo-HSCT in AML is influenced by a variety of factors. The degree of remission before transplantation is a strong predictor of the relapse risk after transplantation. Patients with morphological disease at the time of transplantation have the highest risk of relapse, followed by patients in high-risk remission (CR-HR), while patients in first complete remission (CR1) or second complete remission (CR2) at the time of transplantation have the lowest risk of relapse rate.[17] Studies have shown that *NPM1* and *FLT3* mutational status before transplant are associated with higher relapse risk and poorer outcome in transplant patients, and may serve as useful markers for minimal residual disease (MRD).[17,18] The overexpression of *WT1* before transplant may also represent an MRD tool for risk stratification, and predicts poor survival in AML patients.[19] In addition, pre-transplant bone marrow status is an important prognostic factor for AML patients, as patients with higher marrow blast percentage at transplant usually have higher relapse risk and shorter survival.[20] Some post-transplant factors also influence the prognosis of AML patients undergoing allo-HSCT. The existence of acute and chronic graft versus host disease (GVHD) is associated with higher survival and lower relapse rate in leukemia patients post allo-HSCT, due to the graft versus leukemia (GVL) effect.[21] On the other hand, commonly used chemotherapy drugs for treating AML and transplant conditioning confers increased risk of cardiovascular events (CVEs) after transplant, thereby increasing the risk of death.[22] In our study, we could not control for the above factors and the data were not available from the database. Nonetheless, the two groups, except the difference in *EGFL7* expression levels, were essentially balanced with respect to most of the clinical and molecular characteristics. Both univariate and multivariate analyses indicated that high *EGFL7* expression was an indicator of poor prognosis in transplanted AML patients. This suggests that high *EGFL7* expression may also be a negative prognostic indicator of AML, the same as *FLT3-ITD* and *TP53* mutations.

The role of EGFL7 in tumorigenesis, particularly leukemogenesis, is being defined. A study showed that overexpression of *EGFL7* could promote epidermal growth factor receptor (EGFR) and protein kinase B (AKT) phospho-activation and induce the migration of gastric cancer cells. *EGFL7* knockdown reversed the morphology of epithelial-mesenchymal transition (EMT), decreased vimentin and Snail expression in gastric cancer cell lines.[13] In addition, high expression of *EGFL7* can also promote the migration of human pancreatic cancer cells and act through transcription factors Snail and Slug to induce EMT.[23] These findings suggest that *EGFL7* promotes solid tumor cell metastasis by activating EMT through an EGFR-AKT-Snail signaling pathway. In AML, a study indicated that the AML blasts can synthesize and secrete *EGFL7* protein and promote the leukemic cell growth in an autocrine fashion, suggesting that targeting *EGFL7* may be an effective therapeutic option.[14]

In univariate and multivariate analyses, we also found that *RUNX1* and *TP53* mutations were associated with poor OS, consistent with former findings that somatic mutations in

TP53 and *RUNX1* are indicators of inferior survival in patients with myelodysplastic syndrome, and that mutations in *TP53* and *RUNX1* predict poor outcomes in AML.[24,25] In this study, *FLT3-ITD* was also an independent risk factor for OS, in line with the fact that *FLT3-ITD* is associated with increased risk of relapse in AML.[26] However, *MLL-PTD, NPM1* and *DNMT3A* mutations had no effects on OS in our study. This may be due to the small sample size and the unpredictable interaction of multiple gene mutations. Despite the limitations, *EGFL7* has the potential to become a useful tool in AML risk stratification, especially in patients undergoing allo-HSCT.

In conclusion, our results suggest that high *EGFL7* expression, similar to *FLT3-ITD* and *TP53* mutations, may also predict poor prognosis in AML patients undergoing allo-HSCT. Larger prospective studies are needed to further validate our results.

Abbreviations

AML	acute myeloid leukemia
EGFL7	epithelial growth factor-like 7
CR	complete remission
EFS	event-free survival
OS	overall survival
Allo-HSCT	allogeneic hematopoietic stem cell transplantation
BM	bone marrow
PB	peripheral blood
WBC	white blood cell count
MRD	minimal residual disease
GVHD	graft versus host disease
CVE	cardiovascular event
EMT	epithelial-mesenchymal transition

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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Ethical approval

All data in this study were downloaded from The Cancer Genome Atlas (TCGA) database (https://cancergenome.nih.gov/). We did not involve direct interaction with patients. So, this article does not contain any studies with human participants performed by any of the authors.

ORCID

Zhiheng Cheng http://orcid.org/0000-0001-8837-9542
Yifeng Dai http://orcid.org/0000-0003-3507-7414
Yang Jiao http://orcid.org/0000-0002-1077-6422
Lin Fu http://orcid.org/0000-0002-2416-7572

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