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ARTICLE

Prognostic value of the *FUT* family in acute myeloid leukemia

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Abstract

Genetic abnormalities are more frequently viewed as prognostic markers in acute myeloid leukemia (AML) in recent years. Fucosylation, catalyzed by fucosyltransferases (FUTs), is a post-translational modification that widely exists in cancer cells. However, the expression and clinical implication of the *FUT* family (*FUT1-11*) in AML has not been investigated. From the Cancer Genome Atlas database, a total of 155 AML patients with complete clinical characteristics and *FUT1-11* expression data were included in our study. In patients who received chemotherapy alone showed that high expression levels of *FUT3*, *FUT6*, and *FUT7* had adverse effects on event-free survival (EFS) and overall survival (OS) (all $P < 0.05$), whereas high *FUT4* expression had favorable effects on EFS and OS (all $P < 0.01$). However, in the allogeneic hematopoietic stem cell transplantation (allo-HSCT) group, we only found a significant difference in EFS between the high and low *FUT3* expression subgroups ($P = 0.047$), while other *FUT* members had no effect on survival. Multivariate analysis confirmed that high *FUT4* expression was an independent favorable prognostic factor for both EFS (HR = 0.423, $P = 0.001$) and OS (HR = 0.398, $P < 0.001$), whereas high *FUT6* expression was an independent risk factor for both EFS (HR = 1.871, $P = 0.017$) and OS (HR = 1.729, $P = 0.028$) in patients who received chemotherapy alone. Moreover, we found that patients with low *FUT4* and high *FUT6* expressions had the shortest EFS and OS ($P < 0.05$). Our study suggests that high expressions of *FUT3/6/7* predict poor prognosis, high *FUT4* expression indicates good prognosis in AML; *FUT6* and *FUT4* have the best prognosticating profile among them, but their effects could be neutralized by allo-HSCT.

Introduction

Acute myeloid leukemia (AML) is a heterogeneous group of hematopietic malignancies originating from myeloid progenitors or myeloid-primed multipotential progenitors. It is characterized by the leukemia cells' unchecked

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proliferation, abnormal differentiation, and aggressive infiltration of peripheral blood, bone marrow, or other tissues [1, 2]. The leukemogenesis and the clinical behavior of AML is dominated by the intricate molecular abnormalities and cytogenetics—many of them have been identified as independent prognostic markers, inducing abnormal expression of downstream genes and disrupting the transcriptional regulation systems [3, 4]. For instance, *TET2* and *FLT3* mutations may work synergistically in stimulating the leukemia cell proliferation, which explains their roles as poor prognostic indicators [5, 6]. On the other hand, another two common genetic abnormalities, *CEBPA* and *NPM1* mutations, indicate good prognosis in AML [7, 8]. Gene expression abnormalities exert profound impacts on therapy response and treatment outcomes. Previous studies observed that in AML, high expressions of *FHL2*, *iASPP*, *DOK4*, and *DOK5* act as adverse prognostic factors, and high *DOK7* expression is a good prognostic factor, however, their prognostic effects might overcome by allogeneic hematopoietic stem cell transplantation (allo-HSCT) [9, 10]. Therefore, researchers have been looking for the missing pieces in AML genetic expression profiling to improve the risk classification and individualized treatment for patients.

Fucosylation is a post-translational modification widely existing in proliferating cancer cells, catalyzed by fucosyltransferases (FUTs) [11, 12]. FUT family, including FUT1 to FUT11, are fucosylation synthases which are responsible for adding fucose to oligosaccharide chains of glycolipids, oligosaccharides, and glycoproteins [11, 13]. Fucosylated oligosacharides participate in multiple cell–cell interactions during cell development, differentiation, and malignant transformation [13, 14]. Knocking down the *FUT* genes can potentially inhibit the biosynthesis of certain oligosaccharide chains on tumor cell surface, making them desirable therapeutic targets [15, 16]. According to previous studies, high expressions of *FUT1* and *FUT2* in human ovarian carcinoma-derived RMG-1 cells can promote cell proliferation and resistance to anticancer drugs [17, 18]. Increasing *FUT4* or *FUT7* expression can accelerate hepatocellular carcinoma cell proliferation [19, 20]. Decreasing *FUT3* or *FUT6* expression suppress colon carcinoma cell proliferation [21]. In addition, *FUT8* is highly expressed in the very aggressive human hepatocellular carcinoma cell line HCCLM3 [22].

Nevertheless, the clinical and prognostic value of the *FUT* family in AML remains unknown. The purpose of this study is to explore the impact of the *FUT* family's expression levels on the survival of AML patients who either received chemotherapy alone or followed by allo-HSCT.

Patients and Methods

Patients

The Cancer Genome Atlas (TCGA) database (https://cancergenome.nih.gov/) was screened for patients with complete *FUT* family (*FUT1-11*) expression data [23]. A total of 155 AML patients were included in this study, 84 patients received chemotherapy only and 71 patients received allo-HSCT. The baseline clinical and molecular characteristics, follow-up survival data were public accessible from the database, including age, sex, race, white blood cell (WBC) counts, peripheral blood (PB) and bone marrow (BM) blast percentages, French-American-British (FAB) subtypes, karyotype, cytogenetic risk categorization, and the frequencies of known recurrent genetic mutations/fusions. All patients provided informed consent. This study was approved by the Washington University Human Studies Committee.

Statistical analysis

Descriptive statistics were used to display the clinical and molecular characteristics of patients. The Chi-square test and the Mann–Whitney *U* test were used to compare categorical data and numerical data between groups, respectively. Event-free survival (EFS) and overall survival (OS) were the endpoints of this study. EFS was defined as the time from diagnosis to the first event, including death, and relapse, or was censored at the last follow up. OS was defined as the time from diagnosis to death from any cause or the last follow-up. Kaplan–Meier method and the log-rank test were used to estimate and compare survival. Multivariate Cox proportional hazard models were constructed for EFS and OS using a limited backward elimination procedure [24]. A two-tailed $P < 0.05$ was considered statistically significant. All above statistical analyses were performed by the SPSS 24.0 statistical software, and the GraphPad Prism 7.0 software was used for graphics.

Results

The prognostic value of *FUT* family's expression levels in AML

In order to estimate the prognostic value of *FUT* family in AML patients who underwent chemotherapy alone or received allo-HSCT, both treatment groups were divided into high and low expression subgroups by the median expression levels of each *FUT* members (*FUT1-11*). The

Table 1 Comparison of EFS and OS between the high and low expression levels of the *FUT* family

Variables	EFS		OS	
	χ^2	*P*-value	χ^2	*P*-value
Chemotherapy-only group				
FUT1 (high vs. low)	1.015	0.314	1.429	0.232
FUT2 (high vs. low)	0.194	0.660	0.222	0.638
FUT3 (high vs. low)	7.595	0.006	6.497	0.011
FUT4 (high vs. low)	11.910	0.001	13.273	<0.001
FUT5 (high vs. low)	0.733	0.392	0.694	0.405
FUT6 (high vs. low)	5.365	0.021	4.141	0.042
FUT7 (high vs. low)	6.863	0.009	8.967	0.003
FUT8 (high vs. low)	0.010	0.919	0.311	0.577
FUT10 (high vs. low)	0.000	0.993	0.083	0.774
FUT11 (high vs. low)	0.106	0.745	0.015	0.901
Allo-HSCT group				
FUT1 (high vs. low)	0.950	0.330	1.419	0.234
FUT2 (high vs. low)	0.141	0.707	1.268	0.260
FUT3 (high vs. low)	3.931	0.047	0.739	0.390
FUT4 (high vs. low)	0.314	0.575	0.835	0.361
FUT5 (high vs. low)	0.432	0.511	0.144	0.704
FUT6 (high vs. low)	0.726	0.394	0.067	0.795
FUT7 (high vs. low)	0.027	0.870	0.541	0.462
FUT8 (high vs. low)	0.002	0.968	0.015	0.902
FUT10 (high vs. low)	0.414	0.520	0.045	0.833
FUT11 (high vs. low)	0.134	0.714	0.326	0.568

EFS event-free survival, *OS* overall survival, *Allo-HSCT* allogeneic hematopoietic stem cell transplantation

differences of EFS and OS between high and low expression subgroups were presented in Table 1. In the chemotherapy-only group, high expression levels of *FUT3*, *FUT6*, and *FUT7* adversely affected both EFS and OS (all $P < 0.05$, Fig. 1a, b, e, f), while high *FUT4* expression had favorable effects on EFS and OS (all $P < 0.01$, Fig. 1c, d). However, in the allo-HSCT group, only *FUT3* expression affected EFS ($P = 0.047$), while the expression levels of other *FUT* members were independent of survival.

Relationship between *FUT3/4/6/7* expressions and other patient characteristics in the chemotherapy-only group

As shown in Table 2 and Table 3, the clinical and molecular characteristics of high and low *FUT3/4/6/7* expression subgroups were compared. The $FUT3^{high}$ group had more FAB-M1 ($P = 0.010$) and fewer FAB-M4 patients ($P = 0.040$), more patients with complex karyotype ($P = 0.024$), and more frequent *TP53* mutation ($P = 0.004$). No significant differences were observed in age, gender and race distributions, WBC count, BM blasts, PB blasts, other FAB subtypes, risk stratification, frequencies of other genetic mutations (*FLT3-ITD*, *NPM1*, *DNMT3A*, *IDH1/IDH2*, *RUNX1*, *NRAS/KRAS*, *TET2*, and *MLL*), or relapse rates between the $FUT3^{high}$ and $FUT3^{low}$ groups.

Compared with the $FUT4^{low}$ subgroup, the $FUT4^{high}$ subgroup were younger ($P = 0.033$), had more FAB-M4 patients ($P = 0.002$), more patients with normal karyotype ($P = 0.029$) or *MLL* fusion ($P = 0.024$), but higher relapse ratio ($P = 0.042$). No significant differences were noticed in gender or race distributions, WBC count, BM blasts, PB blasts, other FAB subtypes, risk stratification, or the frequencies of other genetic mutations (*FLT3-ITD*, *NPM1*, *DNMT3A*, *IDH1/IDH2*, *RUNX1*, *NRAS/KRAS*, *TET2*, and *TP53)* between the two subgroups.

Compared with $FUT6^{low}$ subgroup, the $FUT6^{high}$ subgroup had higher percentage of PB blasts ($P = 0.004$), more FAB-M1 and fewer FAB-M4 patients (all $P = 0.040$), more patients with complex karyotype ($P = 0.024$), fewer good-risk patients ($P = 0.013$), and more frequent *TP53* mutations ($P = 0.024$). There were no significant differences in age, gender and race distributions, WBC count, BM blasts, other FAB subtypes, frequency of other genetic mutations (*FLT3-ITD*, *NPM1*, *DNMT3A*, *IDH1/IDH2*, *RUNX1*, *NRAS/KRAS*, *TET2*, and *MLL)*, or relapse rates between the two subgroups.

In regard to *FUT7* expression, the $FUT7^{high}$ subgroup had more WBC count ($P = 0.038$), more patients with normal karotype ($P = 0.029$), fewer patients with *CBFβ-MYH11* or *RUNX1-RUNX1T1* (all $P = 0.026$), and fewer good-risk patients ($P < 0.001$) than the low expression counterpart. Similar to the other three *FUT*s, no significant differences were found in age, gender and race distributions, BM and PB blasts, FAB subtypes, frequency of common genetic mutations (*FLT3-ITD*, *NPM1*, *DNMT3A*, *IDH1/IDH2*, *RUNX1*, *NRAS/KRAS*, *TET2, TP53*, and *MLL*), and relapse rates between the two *FUT7* expression subgroups.

Multivariate analysis of possible prognostic factors in the chemotherapy-only group

To further evaluate the prognostic significance of *FUT3/4/6/7* in patients who received chemotherapy alone, we selected multiple variables, including the expression levels of *FUT3/4/6/7* (high vs. low), age (≥60 vs. <60 years), WBC count (≥15 vs. $< 15 \times 10^9$/L), BM blasts (≥70 vs. <70%), PB blasts (≥20 vs. <20%), *FLT3-ITD* (positive vs. negative), *NPM1* (mutated vs. wild), *DNMT3A* (mutated vs. wild), *RUNX1* (mutated vs. wild), and *TP53* (mutated vs. wild), to construct multivariate Cox proportional hazard models (Table 4).

Results indicated that high *FUT4* expression was an independent favorable factor for EFS (HR = 0.423, $P = 0.001$) and OS (HR = 0.398, $P < 0.001$), whereas high *FUT6* expression, age ≥ 60 years, BM blasts ≥ 70%, and

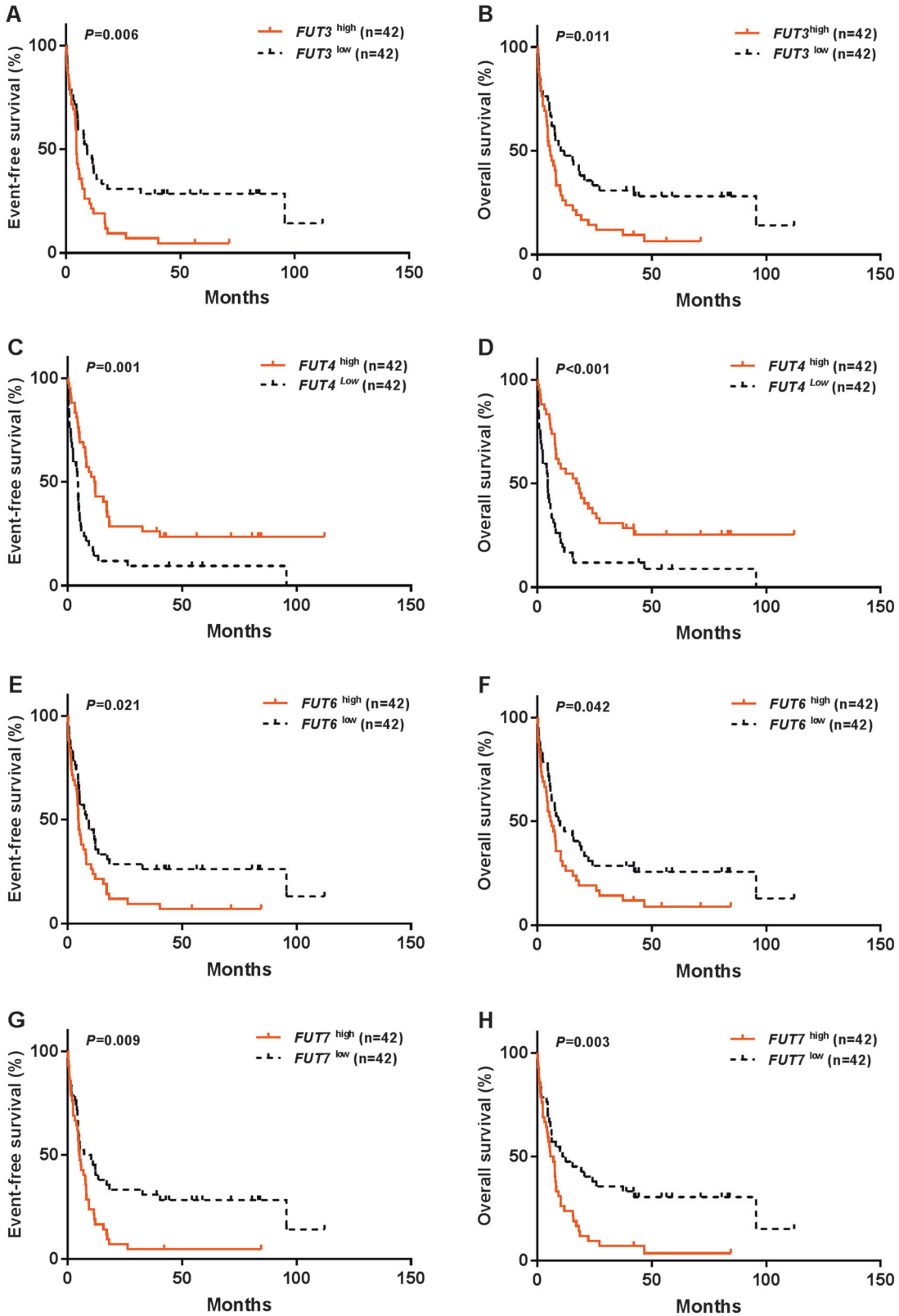

Fig. 1 Kaplan-Meier curves of EFS and OS in patients who received chemotherapy alone by univariate analysis. **a**, **b** High *FUT3* expressers had shorter EFS and OS than the low expressers. **c**, **d** High *FUT4* expressers had longer EFS and OS than the low expressers. **e**, **f** High *FUT6* expressers had shorter EFS and OS than the low expressers. **g**, **h** High *FUT7* expressers had shorter EFS and OS than the low expressers

Table 2 Comparison of the clinical and molecular characteristics between high and low *FUT3* and *FUT4* expression subgroups among patients who received chemotherapy alone

Characteristics	*FUT3*			*FUT4*		
	High ($n = 42$)	Low ($n = 42$)	*P*-value	High ($n = 42$)	Low ($n = 42$)	*P*-value
Age/years, median (range)	68.0 (34.0, 88.0)	64.0 (22.0, 82.0)	0.354*	63.0 (25.0, 81.0)	70.5 (22.0, 88.0)	0.033*
Age group/*n* (%)			0.157§			0.345§
<60 years	10 (23.8)	16 (38.1)		15 (35.7)	11 (26.2)	
≥60 years	32 (76.2)	26 (61.9)		27 (64.3)	31 (73.8)	
Gender/*n* (%)			0.512§			0.126§
Male	21 (50.0)	24 (57.1)		26 (61.9)	19 (45.2)	
Female	21 (50.0)	18 (42.9)		16 (38.1)	23 (54.8)	
Race/*n* (%)						0.450§
Caucasian	31 (73.8)	32 (76.2)	0.801§	33 (78.6)	30 (71.4)	
Others	11 (26.2)	10 (23.8)		9 (21.4)	12 (28.6)	
WBC/$\times 10^9$/L, median (range)	11.0 (0.7, 171.9)	18.7 (1.0, 297.4)	0.231*	16.1 (2.1, 131.5)	10.5 (0.7, 297.4)	0.458*
BM blasts/%, median (range)	72.5 (32.0, 98.0)	71.5 (30.0, 99.0)	0.865*	73.5 (30.0, 98.0)	69.5 (32.0, 99.0)	0.366*
PB blasts/%, median (range)	49.0 (0.0, 97.0)	16.0 (0.0, 98.0)	0.075*	23.0 (0.0, 97.0)	24.0 (0.0, 98.0)	0.921*
FAB subtypes/*n* (%)						
M0	5 (11.9)	2 (4.8)	0.433§	1 (2.4)	6 (14.3)	0.109§
M1	15 (35.7)	5 (11.9)	0.010§	9 (21.4)	11 (26.2)	0.608§
M2	10 (23.8)	11 (26.2)	0.801§	9 (21.4)	12 (28.6)	0.450§
M4	6 (14.3)	14 (33.3)	0.040§	16 (38.1)	4 (9.5)	0.002§
M5	3 (7.1)	9 (21.4)	0.061§	7 (16.7)	5 (11.9)	0.533§
M6	0 (0.0)	1 (2.4)	1.000§	0 (0.0)	1 (2.4)	1.000§
M7	3 (7.1)	0 (0.0)	0.241§	0 (0.0)	3 (7.1)	0.241§
Cytogenetics/*n* (%)						
Normal	18 (42.9)	22 (52.4)	0.382§	25 (59.5)	15 (35.7)	0.029§
t(9;22)/*BCR-ABL1*	1 (2.4)	0 (0.0)	1.000§	0 (0.0)	1 (2.4)	1.000§
inv(16)/*CBFβ-MYH11*	1 (2.4)	5 (11.9)	0.202§	2 (4.8)	4 (9.5)	0.676§
Complex	9 (21.4)	2 (4.8)	0.024§	3 (7.1)	8 (19.0)	0.106§
11q23/*MLL*	1 (2.4)	2 (4.8)	1.000§	3 (7.1)	0 (0.0)	0.241§
-7/7q-	3 (7.1)	0 (0.0)	0.241§	0 (0.0)	3 (7.1)	0.241§
t(8;21)/*RUNX1-RUNX1T1*	3 (7.1)	3 (7.1)	1.000§	4 (9.5)	2 (4.8)	0.676§
Others	6 (14.3)	8 (19.0)	0.558§	5 (11.9)	9 (21.4)	0.242§
Risk/*n* (%)						
Good	4 (9.5)	8 (19.0)	0.212§	6 (14.3)	6 (14.3)	1.000§
Intermediate	21 (50.0)	25 (59.5)	0.381§	25 (59.5)	21 (50.0)	0.381§
Poor	16 (38.1)	8 (19.0)	0.053§	11 (26.2)	13 (31.0)	0.629§
FLT3/*n* (%)			0.606§			0.291§
FLT3-ITD	9 (21.4)	6 (14.3)		9 (21.4)	6 (14.3)	
FLT3-TKD	4 (9.5)	3 (7.1)		5 (11.9)	2 (4.8)	
Wild type	29 (69.0)	33 (78.6)		28 (66.7)	34 (81.0)	
NPM1/*n* (%)			0.102§			0.243§
Mutation	10 (23.8)	17 (40.5)		16 (38.1)	11 (26.2)	
Wild type	32 (76.2)	25 (59.5)		26 (61.9)	31 (73.8)	
DNMT3A/*n* (%)			0.221§			0.807§
Mutation	14 (33.3)	9 (21.4)		11 (26.2)	12 (28.6)	
Wild type	28 (66.7)	33 (78.6)		31 (73.8)	30 (71.4)	

Table 2 (continued)

Characteristics	*FUT3*			*FUT4*		
	High ($n = 42$)	Low ($n = 42$)	*P*-value	High ($n = 42$)	Low ($n = 42$)	*P*-value
IDH1/IDH2/n (%)						
Mutation	7 (16.7)	8 (19.0)	0.776§	8 (19.0)	7 (16.7)	0.776§
Wild type	35 (83.3)	34 (81.0)		34 (81.0)	35 (83.3)	
RUNX1/n (%)						0.079§
Mutation	9 (21.4)	5 (11.9)	0.242§	4 (9.5)	10 (23.8)	
Wild type	33 (78.6)	37 (88.1)		38 (90.5)	32 (76.2)	
NRAS/KRAS/n (%)			0.533§			0.533§
Mutation	5 (11.9)	7 (16.7)		7 (16.7)	5 (11.9)	
Wild type	37 (88.1)	35 (83.3)		35 (83.3)	37 (88.1)	
TET2/n (%)			0.106§			0.332§
Mutation	8 (19.0)	3 (7.1)		7 (16.7)	4 (9.5)	
Wild type	34 (81.0)	39 (92.9)		35 (83.3)	38 (90.5)	
TP53/n (%)			0.004§			0.106§
Mutation	10 (23.8)	1 (2.4)		3 (7.1)	8 (19.0)	
Wild type	32 (76.2)	41 (97.6)		39 (92.9)	34 (81.0)	
MLL			0.746§			0.024§
Positive	5 (11.9)	6 (14.3)		9 (21.4)	2 (4.8)	
Negative	37 (88.1)	36 (85.7)		33 (78.6)	40 (95.2)	
Relapse/*n* (%)			0.498§			0.042§
Yes	17 (40.5)	14 (33.3)		20 (47.6)	11 (26.2)	
No	25 (59.5)	28 (66.7)		22 (52.4)	31 (73.8)	

WBC white blood cell, *BM* bone marrow, *PB* peripheral blood, *FAB* French American British

*denotes Mann–Whitney *U* test

§denotes chi-square test

TP53 mutation were independent risk factors for both EFS and OS (all $P < 0.05$). In addition, *DNMT3A* mutation was an independent risk prognostic factor for EFS ($P = 0.026$).

The combined prognostic effect *FUT4* and *FUT6* expression on AML

To further analyze the combined prognostic effects of the two *FUT* members with independent prognostic value, the chemotherapy-only group was further stratified according to the median expression levels of both *FUT4* and *FUT6*. We observed that the $FUT4^{high}FUT6^{low}$ and $FUT4^{high}FUT6^{high}$ subgroups had significantly longer EFS and OS than the $FUT4^{low}FUT6^{high}$ group, especially the former (all $P < 0.01$, Fig. 2a, b).

Discussion

In our study, we found that high expressions of *FUT3/6/7* were poor prognostic indicators, and high *FUT4* expression was a good prognostic factor in AML patients who received chemotherapy alone, but their prognostic effects were not observed in patients who underwent allo-HSCT, suggesting that allo-HSCT may neutralize their prognostic impact.

The relationship between the *FUT*s and tumorigenesis has been described in multiple solid tumors. High expressions of *FUT3* and *FUT6* can promote the expression of Sialy Lewis X (SLe^x), which in turn has a positive impact on the growth and invasion of oral squamous cell carcinoma. Inhibiting fucosylation may be useful to keep cancer stem cells from proliferation and metastatic spread [25]. In human pancreatic cancer cell lines, the N-fucosylation-related genes, *FUT3*, *FUT5*, and *FUT6*, are activated and may explain the elevated fucosylation on the cell surface and promote cancer cell metastasis [26]. The migratory ability of the Capan-1 cells is decreased with downregulated *FUT3*, making it a suitable target for reducing the metastatic virulence of pancreatic cancer [27]. In prostate adenocarcinoma, however, the expression of *FUT3* is lower than benign prostate alteration [28]. Moreover, in colorectal carcinoma patients, low expression of *FUT3* is associated with tumor infiltration and distant metastasis [29]. The dual role of *FUT3* in tumor cells suggests that different kinds of tumor modulate *FUT3* expression differently to acquire the most beneficial and adaptable characteristics during their

Table 3 Comparison of clinical and molecular characteristics between the high and low *FUT6* and *FUT7* expression subgroups among patients who only received chemotherapy alone

Characteristics	*FUT6*			*FUT7*		
	High ($n = 42$)	Low ($n = 42$)	*P*-value	High ($n = 42$)	Low ($n = 42$)	*P*-value
Age/years, median (range)	66.0 (22.0, 82.0)	67.0 (25.0, 88.0)	0.329*	66.0 (33.0, 88.0)	67.0 (22.0, 82.0)	0.671*
Age group/*n* (%)			1.000§			0.637§
<60 years	13 (31.0)	13 (31.0)		12 (28.6)	14 (33.3)	
≥60 years	29 (69.0)	29 (69.0)		30 (71.4)	28 (66.7)	
Gender/*n* (%)			0.512§			0.274§
Male	21 (50.0)	24 (57.1)		25 (59.5)	20 (47.6)	
Female	21 (50.0)	18 (42.9)		17 (40.5)	22 (52.4)	
Race/*n* (%)			0.208§			0.450§
Caucasian	29 (69.0)	34 (81.0)		33 (78.6)	30 (71.4)	
Others	13 (31.0)	8 (19.0)		9 (21.4)	12 (28.6)	
WBC/$\times 10^9$/L, median (range)	21.6 (0.7, 297.4)	12.2 (1.0, 131.5)	0.620*	28.5 (0.7, 297.4)	9.7 (1.0, 171.9)	0.038*
BM blasts/%, median (range)	74.0 (30.0, 99.0)	70.5 (32.0, 98.0)	0.561*	77.0 (30.0, 99.0)	69.5 (32.0, 95.0)	0.312*
PB blasts/%, median (range)	48.5 (0.0, 98.0)	12.0 (0.0, 97.0)	0.004*	33.0 (0.0, 98.0)	20.0 (0.0, 97.0)	0.635*
FAB subtypes/*n* (%)						
M0	4 (9.5)	3 (7.1)	1.000§	3 (7.1)	4 (9.5)	1.000§
M1	14 (33.3)	6 (14.3)	0.040§	11 (26.2)	9 (21.4)	0.608§
M2	13 (31.0)	8 (19.0)	0.208§	9 (21.4)	12 (28.6)	0.450§
M4	6 (14.3)	14 (33.3)	0.040§	11 (26.2)	9 (21.4)	0.608§
M5	3 (7.1)	9 (21.4)	0.061§	8 (19.0)	4 (9.5)	0.212§
M6	0 (0.0)	1 (2.4)	1.000§	0 (0.0)	1 (2.4)	1.000§
M7	2 (4.8)	1 (2.4)	1.000§	0 (0.0)	3 (7.1)	0.241§
Cytogenetics/*n* (%)						
Normal	23 (54.8)	17 (40.5)	0.190§	25 (59.5)	15 (35.7)	0.029§
t(9;22)/*BCR-ABL1*	1 (2.4)	0 (0.0)	1.000§	0 (0.0)	1 (2.4)	1.000§
inv(16)/*CBFβ-MYH11*	1 (2.4)	5 (11.9)	0.202§	0 (0.0)	6 (14.3)	0.026§
Complex	9 (21.4)	2 (4.8)	0.024§	5 (11.9)	6 (14.3)	0.746§
11q23/*MLL*	1 (2.4)	2 (4.8)	1.000§	2 (4.8)	1 (2.4)	1.000§
-7/7q-	3 (7.1)	0 (0.0)	0.241§	1 (2.4)	2 (4.8)	1.000§
t(8;21)/*RUNX1-RUNX1T1*	1 (2.4)	5 (11.9)	0.202§	0 (0.0)	6 (14.3)	0.026§
Others	3 (7.1)	11 (26.2)	0.019§	9 (21.4)	5 (11.9)	0.242§
Risk/*n* (%)						
Good	2 (4.8)	10 (23.8)	0.013§	0 (0.0)	12 (28.6)	< 0.001§
Intermediate	22 (52.4)	24 (57.1)	0.661§	27 (64.3)	19 (45.2)	0.079§
Poor	16 (38.1)	8 (19.0)	0.053§	13 (31.0)	11 (26.2)	0.629§
FLT3/*n* (%)			0.109§			0.291§
FLT3-ITD	11 (26.2)	4 (9.5)		9 (21.4)	6 (14.3)	
FLT3-TKD	4 (9.5)	3 (7.1)		5 (11.9)	2 (4.8)	
Wild type	27 (64.3)	35 (83.3)		28 (66.7)	34 (81.0)	
NPM1/*n* (%)			0.102§			0.102§
Mutation	17 (40.5)	10 (23.8)		17 (40.5)	10 (23.8)	
Wild type	25 (59.5)	32 (76.2)		25 (59.5)	32 (76.2)	
DNMT3A/*n* (%)			0.221§			0.087§
Mutation	14 (33.3)	9 (21.4)		15 (35.7)	8 (19.0)	
Wild type	28 (66.7)	33 (78.6)		27 (64.3)	34 (81.0)	

Table 3 (continued)

Characteristics	*FUT6*			*FUT7*		
	High ($n = 42$)	Low ($n = 42$)	*P*-value	High ($n = 42$)	Low ($n = 42$)	*P*-value
IDH1/IDH2/n (%)			0.776§			0.776§
Mutation	7 (16.7)	8 (19.0)		8 (19.0)	7 (16.7)	
Wild type	35 (83.3)	34 (81.0)		34 (81.0)	35 (83.3)	
RUNX1/n (%)			0.242§			0.558§
Mutation	5 (11.9)	9 (21.4)		8 (19.0)	6 (14.3)	
Wild type	37 (88.1)	33 (78.6)		34 (81.0)	36 (85.7)	
NRAS/KRAS/n (%)			0.212§			0.533§
Mutation	4 (9.5)	8 (19.0)		7 (16.7)	5 (11.9)	
Wild type	38 (90.5)	34 (81.0)		35 (83.3)	37 (88.1)	
TET2/n (%)			0.106§			0.332§
Mutation	8 (19.0)	3 (7.1)		4 (9.5)	7 (16.7)	
Wild type	34 (81.0)	39 (92.9)		38 (90.5)	35 (83.3)	
TP53/n (%)			0.024§			0.746§
Mutation	9 (21.4)	2 (4.8)		5 (11.9)	6 (14.3)	
Wild type	33 (78.6)	40 (95.2)		37 (88.1)	36 (85.7)	
MLL			0.746§			0.106§
Positive	5 (11.9)	6 (14.3)		8 (19.0)	3 (7.1)	
Negative	37 (88.1)	36 (85.7)		34 (81.0)	39 (92.9)	
Relapse/*n* (%)			0.821§			0.821§
Yes	15 (35.7)	16 (38.1)		16 (38.1)	15 (35.7)	
No	27 (64.3)	26 (61.9)		26 (61.9)	27 (64.3)	

WBC white blood cell, *BM* bone marrow, *PB* peripheral blood, *FAB* French American British

*denotes Mann–Whitney *U* test

§denotes chi-square test

Table 4 Multivariate analysis of the potential prognostic factors of EFS and OS in AML patients who received chemotherapy alone

Variables	EFS		OS	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
FUT3 (high vs. Low)		NS		NS
FUT4 (high vs. Low)	0.423 (0.250, 0.715)	0.001	0.398 (0.239, 0.664)	<0.001
FUT6 (high vs. Low)	1.871 (1.116, 3.137)	0.017	1.729 (1.060, 2.821)	0.028
FUT7 (high vs. Low)		NS		NS
Age (≥60 vs. <60 years)	3.041 (1.629, 5.678)	<0.001	2.550 (1.386, 4.693)	0.003
WBC (≥15 vs. $<15 \times 10^9$/L)	1.694 (0.975, 2.943)	0.062		NS
BM blasts (≥70 vs. <70%)	2.518 (1.487, 4.265)	0.001	2.126 (1.281, 3.530)	0.004
PB blasts (≥20 vs. <20%)		NS		NS
FLT3-ITD (positive vs. negative)		NS		NS
NPM1 (mutated vs. wild)		NS		NS
DNMT3A (mutated vs. wild)	1.927 (1.082, 3.429)	0.026		NS
RUNX1 (mutated vs. wild)	1.993 (0.954, 4.164)	0.066		NS
TP53 (mutated vs. wild)	2.645 (1.207, 5.795)	0.015	2.230 (1.094, 4.545)	0.027

EFS Event-free survival, *OS* Overall survival, *HR* hazard ratio, *CI* confidence interval, *WBC* white blood cell, *BM* bone marrow, *PB* peripheral blood

establishment in the primary site and later during metastasis [30]. We found that high *FUT3* expression was more likely to occur in AML patients with complex karyotype and *TP53* mutation, yet its negative prognostic impact on AML was independent, suggesting that *FUT3* may also play a positive role in leukemogenesis.

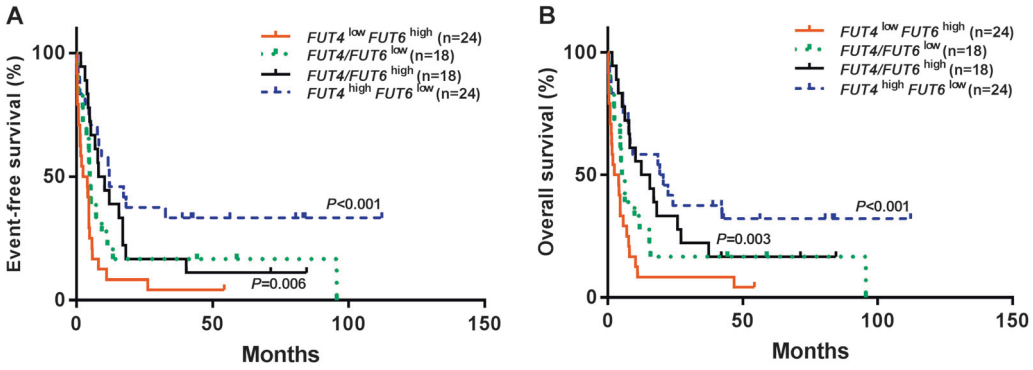

Fig. 2 Comparison of EFS and OS between patients with low or high *FUT4* and *FUT6* expression in univariate analysis. **a**, **b** Patients in the *FUT4*^{low}*FUT6*^{high} groups had shorter EFS and OS than those in the *FUT4*^{high}*FUT6*^{low} and *FUT4/FUT6*^{high} groups

FUT7 controls the progression of the cell cycle via the PLCγ/extracellular signal-regulated kinase signaling pathway in hepatocellular carcinoma [31]. Its overexpression also promotes the occurrence of non-small cell lung cancer by activating the *EGFR/AKT/mTOR* signaling pathway [32]. In AML, our study pointed out that *FUT7* overexpression might also be a tumor-promoting gene, despite its coexistence with other well-known good prognostic factors, such as *CBFβ-MYH11* and *RUNX1-RUNX1T1*.

It has been reported that *FUT6* exhibits a crucial role in mediating the α1,3-fucosylation of glycoprotein during colorectal carcinoma cell and hepatocellular carcinoma cell proliferation [31, 33]. Overexpression of *FUT6* supports the bony metastases of prostate cancer, a biological function alien to both *FUT3* and *FUT7* [34]. On the contrary, Li et al. found that the overexpression of *FUT6*, activated by miR-106b downregulation, can significantly reduce the invasion, migration, and proliferation of human breast cancer cells [35], suggesting that *FUT6* may take part in different biological processes in different cancers. We observed that high *FUT6* expression was an independent adverse prognostic factor for AML patients, and it was associated with complex karyotype, poor cytogenetic risk, and *TP53* mutation, indicating that *FUT6* may be a potential therapeutic target for AML.

FUT4 is highly expressed in both colorectal adenocarcinoma cells and myeloid cells [36]. Studies have shown that high expression of *FUT4* is associated with poor survival in patients with colorectal and lung cancer [37, 38]. In breast cancer, *FUT4* activates the *PI3K/Akt* signaling pathway, leading to multidrug resistance [13]. MiR-26a/26b, miR-125a-5p, and miR-224-3p may also be involved in various *FUT4*-mediated tumorigenic processes [15, 25, 37]. Different from the above results in solid tumor, we found that high expression of *FUT4* was an independent good prognostic factor in AML, and it was associated with younger age and normal karyotype. This indicated that the role of *FUT4* in various diseases may also be different. Furthermore, we found that AML patients with low *FUT4* expression and high *FUT6* expression had the shortest EFS and OS compared to other patients, indicating that the combination of *FUT4* and *FUT6* may be a better tool in AML prognostication. The detailed biological interactions between *FUT4* and *FUT6* are still unknown, but our results suggested that they may play different roles in leukemogenesis although they belong to the same gene family.

In multivariate analysis, age ≥60 years and BM blasts ≥70% were also independent risk factors for AML patients, consistent with previous findings that older AML patients generally have unfavorable prognosis due to poorer baseline performance status, higher mutation burden, and poorer tolerance to chemotherapy, and that abnormal proliferation of BM blasts has apparent adverse effects on survival [39, 40]. We found that mutations in *DNMT3A* and *TP53* were also independent risk factors for AML patients, consistent with other studies [41, 42]. Our results, while confirming previous study results, will help to refine risk stratification and provide evidence for precision medicine in AML.

In summary, our results have shown that high expressions of *FUT3/6/7* indicate poor prognosis, and high *FUT4* expression predicts good prognosis in AML, but their prognostic effects on survival may be neutralized by allo-HSCT. Moreover, *FUT4* and *FUT6* are stronger prognosticators for AML compared with the other *FUT*s, and their combined predictive effect is more prominent. Our study is limited by its small sample size and our results require larger prospective cohorts to verify. The mechanism of the combined action of *FUT4* and *FUT6* in AML needs to be further delineated.

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Compliance with ethical standards

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

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