RESEARCH ARTICLE

Clinical Significance of MAP-7 and FOXC1 in Egyptian Acute Myeloid Leukemia Patients

Safa Mohamed Nabawy[1], Lobna Ahmed Refaat[1], Hussam Mohamed Naser Aldin[2], Reham A Rashed[1]*

Abstract

Purpose: The present study aimed to report the clinical correlations and prognostic significance of microtubule-associated protein-1 (MAP-7) and forkhead box transcription factor-C1 (FOXC1) expression in Egyptian patients with newly diagnosed acute myeloid leukemia (AML). **Methods:** The study included 80 adults with newly diagnosed AML. Laboratory investigations included complete blood count, morphological examination of bone marrow aspirate, immunophenotyping, conventional karyotyping and molecular study for fms-like tyrosine kinase 3 (FLT3), nucleophosmin-1 (NPM1) and CCAAT/enhancer binding protein α (CEBPA) mutations. MAP-7 and FOXC1 expressions in bone marrow were determined using RT-PCR. Patients were followed for a median (range) period of 6.4 (1.0-35) months. The study outcomes included treatment response, progression-free survival (PFS) and overall survival (OS). **Results:** Patients with low FOXC1 expression had significantly lower mortality rate (60.0 % versus 84.6 %, p=0.021), significantly longer PFS duration and significantly longer OS. No significant differences were noted between MAP7 expression groups regarding treatment response, mortality rate, PFS duration and OS duration. Interestingly, a significant direct correlation was noted between FOXC1 and MAP7 expressions (r=0.25, p=0.027). **Conclusions:** FOXC1 and MAP7 expressions are significantly correlated. High expression of FOXC1 in Egyptian population may be related to shorter OS and PFS.

Keywords: Acute myeloid leukemia- MAP-7- FOXC1

Introduction

Acute myeloid leukemia (AML) is a heterogeneous hematologic malignancy characterized by proliferation and aberrant differentiation of immature clonal myeloid cells preventing normal bone marrow hematopoiesis (DiNardo and Cortes, 2016). Identification of genes and cellular pathways active in AML stem cells is essential, both for the understanding of disease biology and also for their evaluation as candidate therapeutic targets (Somerville et al., 2015).

Microtubules constitute a major component of the eukaryotic cytoskeleton. They play important roles in virtually every cellular process, such as cell division, cell motility, intracellular organization and trafficking of organelles. To fulfil these divergent functions, microtubules assemble into distinct arrays characterized by defined architecture and dynamics. Formation of these assemblies requires specialized proteins that interact with microtubules; the microtubule-associated proteins (MAPs) (Bodakuntla et al., 2019).

MAP7 is predominantly expressed in cells of epithelial origin (Bhat and Setaluri, 2007). Some reports have shown its clinical value in several malignancies including colon (Blum et al., 2008), cervical (Zhang et al., 2020a) and gastric (Yu et al., 2021) cancers. Only one study reported its role as an adverse prognostic marker in patients with cytogenetically normal AML. The study attributed this role to the distinctive gene/microRNA expression and related cell signaling pathways. Mircro-RNAs involved in this process included miR-361, miR-194 and miR-196b that targeted toll-like receptor-4 (TLR4), CD86 and Kruppel Like Factor 11 (*KLF11*) genes respectively while syntaxin 11 (*STX11*) gene was targeted by miR-92a and miR-196b (Fu et al., 2016).

Forkhead box transcription factors (FOXs) include a family of transcriptional factors (Myatt and Lam, 2007) involved in many biological processes, including cell proliferation, differentiation, survival, and death (Lam et al., 2013).

The mesenchymal transcription factor FOXC1 is expressed in hematopoietic stem progenitor cells (HSPCs) in the setting of AML but not in normal HSPCs. It was recently demonstrated to play an important role in AML disease onset and progression by blocking myeloid lineage differentiation and enhancing clonogenic potential (Bachu

[1]Department of Clinical Pathology, National Cancer Institute Cairo University, Cairo, Egypt. [2]Department of Medical Oncology, National Cancer Institute Cairo University, Cairo, Egypt. *For Correspondence: reham_r9@yahoo.com

et al., 2016). Similar to MAP-7, only one report discussed the value of FOXC1 expression in AML (Somerville et al., 2015).

Remarkably, FOXC1 was incorporated in upregulation of TLR (Zhang et al., 2019) in myocardial ischemia and was targeted together with KLF11 in the context of prostate cancer immune response (Zhang et al., 2020b).

The present study aimed to report the clinical correlations and prognostic significance of MAP-7 and FOXC1 expression in Egyptian patients with newly diagnosed AML.

Materials and Methods

Patients and Methods

The present study was conducted at National Cancer Institute (NCI), Cairo University during the time period from March 2016 through December of 2018. The study protocol was approved by the ethical committee of NCI in accordance with Helsinki guidelines for protection of human subjects. Written informed consent was obtained from all patients. The study included 80 adult patients with newly diagnosed AML. All patients who were ineligible for induction chemotherapy, received therapy or diagnosed as AML-M3 were excluded from the study.

All patients were subjected to careful history taking, thorough clinical examination and radiological assessment when indicated. Laboratory investigations included complete blood count, morphological examination of bone marrow aspirate, immunophenotyping, conventional karyotyping and molecular study for FLT3, NPM1 and CEBPA mutations as part of the routine diagnostic work-up for suspected AML according to the WHO classification (Arber et al., 2016).

Treatment protocol was divided into two phases as follows: Induction of remission therapy; doxorubicin single dose IV 45 mg/m^2 in the first 1–3 days together with continuous infusion of cytosine arabinoside (100 mg/m^2) in days 1–7. Cytosine arabinoside dose was reduced to 20 mg/m^2/day SC for patients older than 60 years. Bone marrow examination on day 14 provided preview of the response to induction therapy.

Post-remission therapy (remission-consolidation) was risk stratified and additional 3 or more cycles of high-dose cytosine arabinoside and mitoxantrone (HAM regimen) were given according to the estimated risk. Patients were followed for 2 years. Complete remission (CR) at day 28 was defined by morphological recovery of the BM and blood counts. Relapse was defined by ≥ 5% BM blasts, reappearance of circulating leukemic blasts, or development of extra- medullary leukemia (Dohner et al., 2010).

Quantitative measurement of MAP7 and FOXC1 genes By Real- Time PCR
RNA Isolation and Complementary DNA Synthesis

Pretreatment BM samples and controls were collected under complete sterile conditions and extraction of total RNA from leucocytes pellet after erythrocyte lysis was carried using QIA-amp RNA blood Mini Kit for total RNA purification (QIAGEN® Austin, USA cat.

no.52304), following the manufacturer's instructions. The concentration and purity of RNA was measured at 260, 280, and 230 nm using Nano Drop 2000/2000c Spectrophotometer (Thermo Scientific, USA). Ratio of A260/A280 = 1.8 - 2.1 and A260/A230 = 1.8 - 2.1 indicates highly pure RNA.

Conversion of the extracted RNA to cDNA (reverse transcription): using Applied Biosystems™ High-Capacity cDNA Reverse Transcription Kit; (Thermo Fisher Scientific, USA; cat. no. 4368814) according to the assay protocol. PCR reactions were carried out in a total volume of 20ul (10ul mix+ 10ul extracted RNA), Amplification of the cDNA to detect *MAP7* and *FOXC1* genes expression: Real Time PCR (RT-PCR) was performed using the Step One TM Detection System (Applied Biosystems, Ambion, Austin, TX) with a 20 ul reaction mixture including TaqMan® Universal PCR supplied at 2X concentration (Cat. no.:4370048, Thermo Fisher scientific, Applied biosystems, USA). The Taqman primer probe for FOXC1 and MAP7 mRNA are ready made assays (Thermo Fisher Scientific, USA) and GAPDH mRNA was used as a reference gene. The relative expression of both genes was determined using comparative CT method for the samples in relation to expression of *GAPDH* (Δ CT = gene CT – GAPDH CT). The threshold cycle data (Ct) and baselines were determined using auto settings. The relative quantification of MAP7 and FOXC1 expression was calculated using the comparative CT method (2–ΔΔCT) where ΔΔCT is the difference of ΔCT value between the leukemia and the control (ΔΔCT = ΔCT leukemia gene – ΔCT control gene), and ΔCT is the difference of CT value between the target (gene) and endogenous reference (*GAPDH*) gene (ΔCT = CT Target gene – *GAPDH* gene). FOXC1 and MAP7 expressions were categorized into low and high according to a cutoff value of 1.023 and 1.369 respectively based on the best for overall survival.

Patients were followed for a median (range) period of 6.4 (1.0-35) months. One patient was lost to follow up after experiencing disease relapse. The study outcomes included treatment response, progression-free survival (PFS) and overall survival (OS). Data reported in the present study were reported as median and range, number or number and percent. Numerical data were compared using Mann-Whitney U test while categorical data were compared using Fisher's exact test or chi-square test as appropriate. Kaplan-Meier survival analysis with log-rank comparison was used to illustrate PFS and OS of the studied patients. Cox-hazard regression analysis was used to identify predictors of PFS and OS. P value less than 0.05 was considered statistically significant.

Results

The present study included 80 newly diagnosed AML patients. The male: female frequency was 41:39 with a median (range) age of 42.0 (18.0 – 65.0) years. Other clinical and laboratory data of the studied cohort are listed in Table 1.

Comparison between patients with low and high FOXC1 expression revealed significantly higher frequency of lymphadenopathy in the former group (60.0
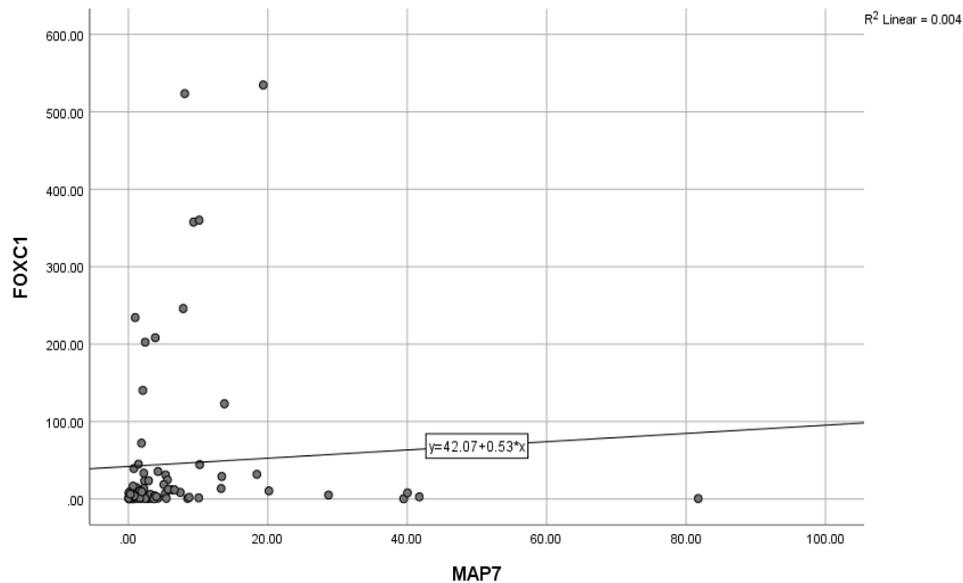
Figure 1. Correlation between MAP-7 and FOXC1 Expression.

% versus 23.1 %, p=0.005). Patients with low expression showed significantly lower frequency for AML M1 disease. Moreover, they had significantly higher frequency of patients with low and intermediate risk groups. It was also shown that patients with low FOXC1 expression had significantly lower mortality rate (60.0 % versus 84.6 %, p=0.021), significantly longer PFS duration [median (95 % CI): 17.0 (0.0-36.0) versus 2.0 (0.9-3.0) months, log-rank p=0.015] and significantly longer OS [median (95 % CI): 10.0 (4.0-17.9) versus 2.0 (0.9-3.1) months, log-rank p=0.04] (Table 1, Figures 1,2).

Comparison between patients with low and high MAP7 expressions revealed significantly higher frequency of lymphadenopathy in the low expression group (47.8 % versus 22.8 %, p=0.027). The same group showed significantly lower frequency for AML M1 disease (8.7 % versus 29.9 %) and significantly higher frequency for M2 disease (52.2 % versus 31.6). It was also noted that the low MAP7 expression group had significantly higher frequency of patients with high risk (34.8 % versus 5.3 %, p=0.002). No significant differences were noted between MAP7 expression groups regarding treatment response, mortality rate, PFS duration and OS duration (Table 2, Figures 3 and 4). Cox-hazard regression analysis identified treatment response as the only predictor of PFS and OS in the studied patients (Tables 3-4). Interestingly, a significant direct correlation was noted between FOXC1 and MAP7 expression (r=0.25, p=0.027) (Figure 5).

Discussion

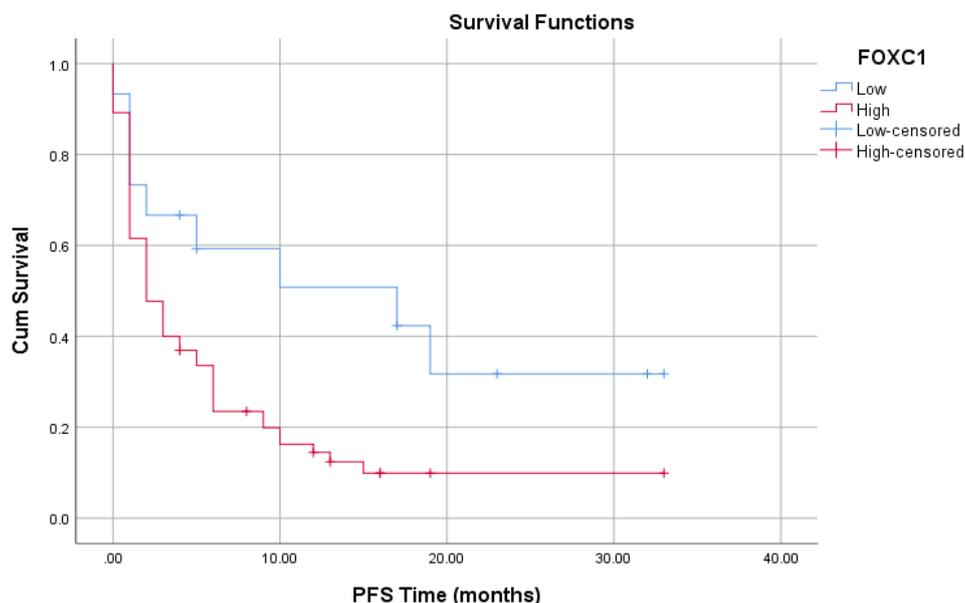Comprehensive genomic profiling at time of diagnosis

Figure 2. PFS in Patients with Low and High FOXC1 Expression.

Table 1. Clinical, Laboratory and Outcome Data of All Patients and Patients with Low and High FOXC1

	All patients N=80	Low FOXC1 n=15	High FOXC1 n=65	p value
Age (years) median (range)	42.0 (18.0 – 65.0)	43.0 (33.0-50.5)	41.0 (30.0-53.0)	0.93
Male/female n	41/39	6-Sep	32/33	0.64
Clinical findings n (%)				
Constitutional symptoms	36 (45.0)	8 (53.3)	28 (43.1)	0.47
Lymphadenopathy	24 (30.0)	9 (60.0)	15 (23.1)	0.005
Hepatosplenomegaly	22 (27.5)	4 (26.7)	18 (27.7)	0.94
Laboratory findings median (range)				
Hemoglobin (gm/dl)	8.0 (6.7-9.0)	8.6 (7.2-10.2)	7.7 (6.6-8.9)	0.18
TLC ($\times 10^3$/ml)	29.5 (8.3-78.5)	30.0 (12.3-139.0)	22.0 (7.9-75.0)	0.24
Platelets count ($\times 10^3$/ml)	34.5 (17.8-50.0)	36.0 (26.5-43.5)	33.0 (15.0-50.0)	0.48
Peripheral blasts (%)	50.0 (30.0-77.0)	67.5 (38.3-77.0)	50.0 (29.0-75.0)	0.39
BM blasts (%)	70.0 (51.8-80.0)	60.0 (42.5-77.5)	70.0 (55.0-80.0)	0.36
BM cellularity n (%)				
Hyper-cellular	65 (81.2)	-	3 (4.6)	0.84
Normo-cellular	12 (15.0)	3 (20.0)	9 (13.8)	
Hypo-cellular	3 (3.8)	12 (80.0)	53 (81.5)	
FAB classification n (%)				
M0	1 (1.3)	-	1 (1.5)	0.045
M1	19 (23.8)	2 (13.3)	17 (26.2)	
M2	30 (37.5)	7 (46.7)	23 (35.4)	
M4	25 (31.3)	4 (26.7)	21 (32.3)	
M5a	1 (1.3)	-	1 (1.5)	
M5b	4 (5.0)	2 (13.3)	2 (3.1)	
Immunophenotyping markers expression n (%)				
CD34	56 (70.0)	11 (73.3)	45 (69.2)	0.76
CD13	68 (85.0)	12 (80.0)	56 (86.2)	0.55
CD33	68 (85.0)	12 (80.0)	56 (86.2)	0.55
MPO	68 (85.0)	12 (80.0)	56 (86.2)	0.55
CD14,4,64	30 (37.5)	6 (40.0)	24 (36.9)	0.82
CD117	29 (36.3)	9 (60.0)	20 (30.8)	0.045
Aberrant lymphoid markers (CD7, 19, 2)	8 (10.0)	2 (13.3)	6 (9.2)	0.63
Cytogenetic and molecular markers n (%)				
Abnormal karyotyping	33 (41.3)	9 (60.0)	24 (36.9)	0.2
t (8;21)	8 (10.0)	3 (20.0)	5 (7.7)	0.15
Inv16	6 (7.5)	1 (6.7)	5 (7.7)	0.89
NPM Mutation	10 (12.5)	2 (13.3)	8 (12.3)	0.91
FLT3 mutation	11 (13.8)	2 (13.3)	9 (13.8)	0.96
Risk stratification n (%)				
Low	34 (42.5)	11 (73.3)	23 (35.4)	0.028
Intermediate	35 (43.8)	3 (20.0)	32 (49.2)	
High	11 (13.8)	1 (6.7)	10 (15.4)	
Treatment response n (%)				
CR	46 (57.5)	11 (73.3)	35 (53.8)	0.17
No CR	34 (42.5)	4 (26.7)	30 (46.2)	
Mortality n (%)	64 (80.0)	9 (60.0)	55 (84.6)	0.021
PFS (months) median (95% CI)	3.0 (1.8-4.2)	17.0 (0.0-36.0)	2.0 (0.9-3.0)	0.015
OS (months) median (95% CI)	3.0 (1.5-4.5)	10.0 (4.0-17.9)	2.0 (0.9-3.1)	0.04

BM, Bone marrow; CR, Complete response; FLT3, fms-like tyrosine kinase 3; MPO,Myeloperoxidase; NPM1, Nucleophosmin-1; OS. Overall survival; PFS, Progression-free survival; TLC, Total leukocytic count

Table 2. Clinical, Laboratory and Outcome Data of Patients with Low and High MAP7

	Low MAP7 n=23	High MAP7 n=57	p value
Age (years) median (range)	43.0 (31.5-50.5)	41.0 (30.0-53.0)	0.78
Male/female n	15/8	26/31	0.18
Clinical findings n (%)			
Constitutional symptoms	12 (52.2)	24 (42.1)	0.41
Lymphadenopathy	11 (47.8)	13 (22.8)	0.027
Hepatosplenomegaly	6 (26.1)	16 (28.1)	0.86
Laboratory findings median (range)			
Hemoglobin (gm/dl)	8.5 (7.2-9.2)	7.7 (6.5-9.0)	0.23
TLC (×10³/ml)	50.0 (13.0-132.0)	18.0 (6.7-69.0)	0.055
Platelets count (×10³/ml)	35.0 (20.0-47.5)	33.0 (16.0-50.0)	0.95
Peripheral blasts (%)	50.0 (33.0-77.0)	50.0 (29.5-85.5)	0.82
BM blasts (%)	52.0 (42.5-74.0)	72.0 (60.0-81.0)	0.023
BM cellularity n (%)			
Hyper-cellular	-	3 (5.3)	0.68
Normo-cellular	4 (17.4)	8 (14.0)	
Hypo-cellular	19 (82.6)	46 (80.7)	
FAB classification n (%)			
M0	-	1 (1.8)	0.001
M1	2 (8.7)	17 (29.9)	
M2	12 (52.2)	18 (31.6)	
M4	7 (30.4)	18 (31.6)	
M5a	-	1 (1.8)	
M5b	2 (8.7)	2 (3.5)	
Immunophenotyping markers expression n (%)			
CD34	14 (60.9)	42 (73.7)	0.26
CD13	16 (69.6)	52 (91.2)	0.014
CD33	16 (69.6)	52 (91.2)	0.014
MPO	16 (69.6)	52 (91.2)	0.014
CD14,4,64	8 (34.8)	22 (38.6)	0.75
CD117	11 (47.8)	18 (31.6)	0.17
Aberrant lymphoid markers (CD7, 19, 2)	4 (17.4)	4 (7.0)	0.16
Cytogenetic and molecular markers n (%)			
Abnormal karyotyping	13 (56.5)	20 (35.1)	0.078
t (8;21)	4 (17.4)	4 (7.0)	0.16
Inv16	1 (4.4)	5 (8.8)	0.5
NPM Mutation	4 (17.4)	6 (10.5)	0.4
FLT3 mutation	3 (13.0)	8 (14.0)	0.91
Risk stratification n (%)			
Low	9 (39.1)	25 (43.9)	0.002
Intermediate	6 (26.1)	29 (50.9)	
High	8 (34.8)	3 (5.3)	
Treatment response n (%)			
CR	16 (69.6)	30 (52.6)	0.17
No CR	7 (30.4)	27 (47.4)	
Mortality n (%)	16 (69.6)	48 (84.2)	0.24
PFS (months) median (95% CI)	6.0 (3.1-8.9)	2.0 (0.9-3.1)	0.17
OS (months) median (95% CI)	6.0 (0.2-11.8)	2.0 (0.9-3.1)	0.095

BM, Bone marrow; CR, Complete response; FLT3, fms-like tyrosine kinase 3; MPO,Myeloperoxidase; NPM1, Nucleophosmin-1; OS. Overall survival; PFS, Progression-free survival; TLC, Total leukocytic count
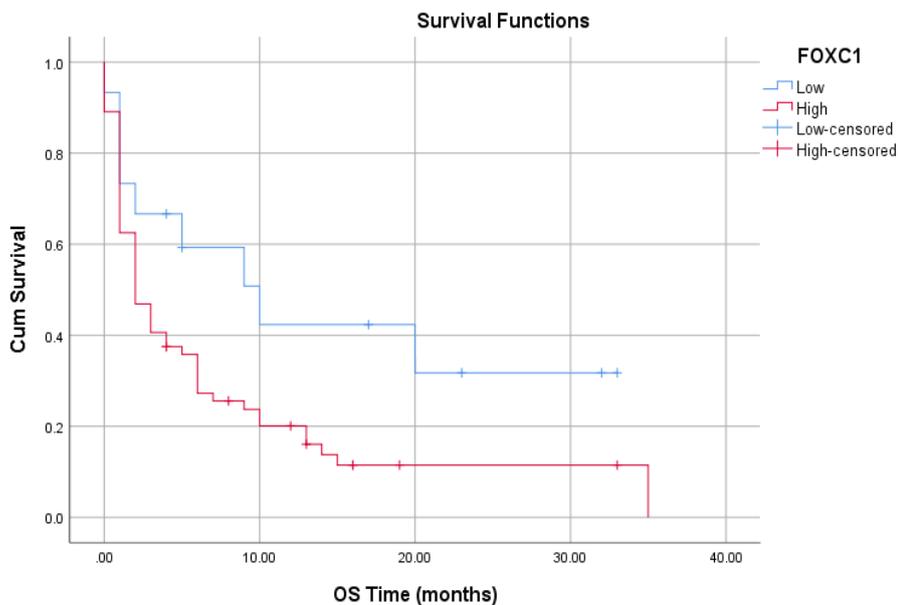
Figure 3. OS in Patients with Low and High FOXC1 Expression

can be useful for AML classification, risk stratification, prognosis and ultimately allows for more selective therapeutic interventions. In this study, we analyzed the expression of novel biomarkers FOXC1 and MAP7 genes by RT-PCR to evaluate their clinical and prognostic significance in 80 newly diagnosed AML patients. We

Table 3. Predictors of Progression-Free Survival in the Studied Patients

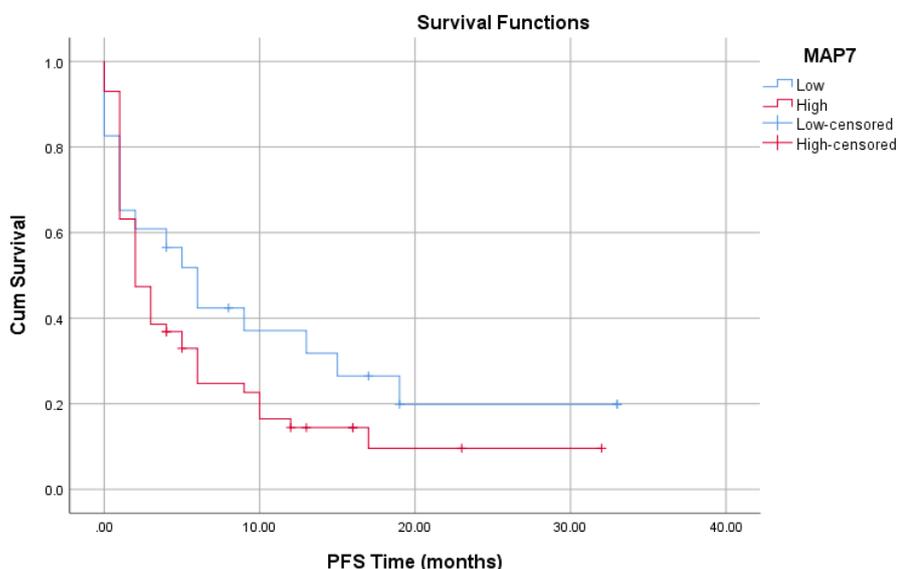|	Univariate analysis			Multivariate analysis		
	HR	95%CI	P	HR	95%CI	p
Age	1.01	0.99-1.03	0.23	-	-	-
Sex	0.93	0.57-1.51	0.76	-	-	-
Risk						
Intermediate	1.19	0.7-2.03	0.53	-	-	-
High	1.39	0.68-2.82	0.37	-	-	-
Treatment response	5.8	3.2-10.5	<0.001	5.8	3.2-10.5	<0.001
FOXC1 expression	1	0.99-1.0	0.22	-	-	-
MAP7 expression	1.01	0.99-1.03	0.12	-	-	-

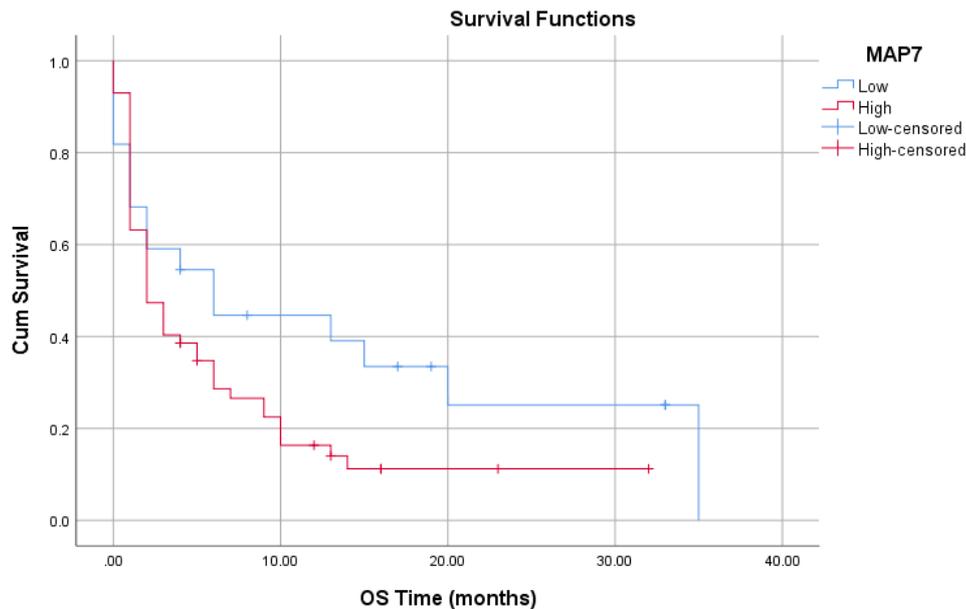Figure 4. PFS in Patients with Low and High MAP-7 Expression

Figure 5. OS in Patients with Low and High MAP-7 Expression.

Table 4. Predictors of Overall Survival in the Studied Patients

	Univariate analysis			Multivariate analysis		
	HR	95%CI	P	HR	95%CI	p
Age	1.01	0.99-1.03	0.26	-	-	-
Sex	0.87	0.53-1.44	0.6	-	-	-
Risk						
Intermediate	1.2	0.7-2.06	0.51	-	-	-
High	1.24	0.6-2.6	0.56	-	-	-
Treatment response	6.2	3.4-11.2	<0.001	6.2	3.4-11.2	<0.001
FOXC1 expression	1	0.99-1.0	0.19	-	-	-
MAP7 expression	1.01	0.99-1.03	0.16	-	-	-

didn't detect FOXC1 or MAP7 mRNA transcripts by real time PCR in normal bone marrow cells from any of the 40 healthy controls.

In Egypt, treatment of AML is very challenging. Although we apply the same protocol of treatment of AML used worldwide; response of our patients to treatment as well as death rates greatly differ. That's why we search and investigate for novel prognostic markers. Such biomarkers can be useful indicators for risk stratification and can provide insight into the pathogenesis of AML and thus inspire novel targeted therapies. Up to our knowledge these 2 genes: *FOXC1* and *MAP7* haven't been studied before in the Egyptian population.

In the present study, patients with low FOXC1 expression showed significantly lower frequency of M1 disease. Moreover, they had significantly higher frequency of patients with low and intermediate risk groups in line with the conclusions of Somerville et al., (Somerville et al., 2015).

While the present study failed to document a relation between FOXC1 expression and treatment response, the study of Somerville et al., (Somerville et al., 2015) found that FOXC1 expression was significantly elevated in non-responders to induction chemotherapy.

In the current study, it was shown that patients with low FOXC1 expression had significantly lower mortality rate, significantly longer PFS duration and significantly longer OS. These results are in agreement with Somerville et al., (Somerville et al., 2015) who found that FOXC1 expression in AML is an independent prognostic predictor of decreased OS and PFS. Of note, the present study failed to confirm such findings in multivariate analysis.

In our study, we found that high MAP7 expression was associated with significantly higher BM blast % which is a novel finding. In addition, we noted that patients with low MAP7 expression showed significantly lower frequency of M1 disease and significantly higher frequency of M2 disease. These results are close to those of Fu et al., (2016) who found that the most frequent subtype among high MAP7 was M1 followed by M2.

In our study, there no relation between MAP7 expression and survival. These results were in contrast with Fu et al., (2016) who reported that high MAP7 expression was associated with worse OS.

Interestingly, the present study found a significant correlation between *FOXC1* and *MAP7* genes expression in AML patients. This may indicate a cross-talk between the two genes in the pathogenic development of AML

which needs to be elucidated by further studies.

In conclusion of this study, high expression of FOXC1 in Egyptian population was significantly associated with shorter OS and PFS. FOXC1 and MAP7 are notably under-studied in AML and should have more interest.

Author Contribution Statement

All the listed authors have contributed substantially to the production of this research work.

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None.

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