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Prognostic value of bone marrow MUC4 expression in acute myeloid leukaemia

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ABSTRACT

Background: Aberrant expression of mucin-4 (MUC4) is present in a variety of solid cancers, but the expression pattern of *MUC4* and its clinical relevance in acute myeloid leukaemia (AML) is unknown. We aimed to evaluate the expression level of *MUC4* and explore its prognostic value in newly diagnosed adult patients with AML.

Methods: Bone marrow from 70 AML patients and 26 healthy donors was obtained. *MUC4* levels were quantified by quantitative real-time PCR. Routine blood indices were measured by standard techniques.

Results: Bone marrow *MUC4* expression levels were significantly elevated in AML patients compared to controls at median (range) 2.77 (0.7–16.6) and 1.14 (0.5–1.99) respectively ($p = 0.005$). Moreover, lower *MUC4* expression was strongly associated with persistent remission ($p = 0.001$) while higher *MUC4* levels were associated with worse overall as well as disease-free survival ($p = 0.011$ and $p = 0.006$, respectively). Thus, its level may act as an indicator of disease progression. High *MUC4* expression was identified as an independent prognostic predictor for both overall survival and disease-free survival.

Conclusion: *MUC4* over-expression is an independent predictor of a poor prognosis in AML patients.

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KEYWORDS
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Introduction

Acute myeloid leukaemia (AML) is a common acute leukaemia that affects adults, it is an aggressive haematological malignancy caused by several factors including environmental factors, chromosomal aberrations, and gene mutations. AML is a cytogenetically, and molecularly heterogeneous disease characterized by over-proliferation and accumulation of myeloid blasts in the bone marrow and blood [1,2]. Though the survival rate in AML has improved, relapse remains a major obstacle towards treatment [3] and the prognosis assessment of AML is still difficult. Therefore, identifying an effective and novel marker for the diagnosis and prognosis of clinical outcome and treatment response is vital.

Mucins are a heterogeneous family of high molecular weight glycoproteins that have been subdivided into three types: secretory (gel-forming), membrane-bound, and soluble mucins [4]. They are produced from various types of epithelial cells and leukocytes and play an important role in lubrication and protection from microbial pathogens [5,6]. Additionally, mucins participate in several signalling pathways to regulate cellular renewal, cell–cell interactions, differentiation, and apoptosis [7,8].

MUC4 is located at chromosome locus 3q29 and encodes the multi-domains transmembrane protein mucin-4 (MUC4) [9]. With its epidermal growth factor (EGF)-like domains, MUC4 binds to erythroblastic oncogene B2 (ErbB2) receptor tyrosine kinase, also known as epidermal growth factor receptor (HER2), to facilitate signal transduction, cell proliferation, and cell survival [10–12].

Although several studies on solid cancers have implicated MUC4 expression in diagnosis and disease progression, data about its levels and prognostic value are largely inconclusive. MUC4 is over-expressed in breast and pancreatic cancers, while its expression level is decreased in prostatic adenocarcinoma and bladder cancer [13–16]. Although the prognostic significance of MUC4 varies with the cancer type, MUC4 expression is associated with tumour aggressiveness and poor survival in lung and ovarian cancers [17,18], whilst in mucoepidermoid carcinoma of salivary glands, MUC4 expression is related to better survival [19].

Although *MUC4* is significantly mutated in whole-exome analysis of normal karyotypes, indicating that *MUC4* might be a predictor for the risk of normal karyotype AML [20], the prognostic utility of *MUC4* in AML is unknown. We, therefore, hypothesised the alteration of *MUC4* expression level in the bone marrow of adult AML patients and its potential utility as a prognostic marker.

Materials and methods

We recruited 70 newly diagnosed adult AML patients from the medical oncology department, National Cancer Institute, Cairo University, Cairo, Egypt, who

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were treated and followed up between May 2016 and October 2019, while acute promyelocytic leukaemia (M3) subtype patients received different treatment protocols; thus, they were excluded from this study. All AML cases were diagnosed according to criteria of the French-American-British (FAB) classification and WHO combined with immunological and cytogenetic analyses [21]. Twenty-six age and sex-matched healthy donors (donors of a bone marrow transplant) with no clinical symptoms of haematologic or other types of cancer and other diseases were enrolled. Bone marrow (BM) aspiration specimens were collected into EDTA from all participants. This study was approved by the Ethics Committee and Institutional Review Board of National Cancer Institute, Cairo University (201617027–-4). All participants signed written informed consent following the Declaration of Helsinki guidelines.

AML patients received induction chemotherapy consisting of the standard 3 + 7 regimen (Doxorubicin 30 mg/m^2 on 1–3 days; Cytarabine 100 mg/m^2 on 1–7 days). By the end of first induction therapy, complete remission (CR) was defined by normalization of bone marrow (BM) elements; neutrophil count of 1×10^9/L and platelet count of 100×10^9/L, and BM examination showing a normocellular marrow containing less than 5% blasts. Resistant disease was defined as the presence of more than 25% blasts in BM. Overall survival (OS) was the time from the entry into the study to death and disease-free survival (DFS) was the time from the date of CR achievement to death or relapse.

Total RNA was extracted from bone marrow cells using QIAamp® RNA Blood Mini Kits (Cat# 52304, Qiagen, Germany) based on the manufacturer's instructions. The purity and the concentration of the purified RNA were detected using Nano-Drop (Quawell, Q-500, Scribner, USA). The synthesis of cDNA was performed by reverse transcription using High-Capacity cDNA Reverse Transcription Kit (Cat# 4368814, Thermo Fisher) and stored at – 20°C till performing quantitative real-time PCR.

Real-time quantitative PCR was carried out to evaluate the expression of MUC4 and GAPDH (as internal control) using Step One™ Real-Time PCR System (Applied Biosystems). The real-time PCR reactions were performed in a 20 µL volume using TaqMan™ Universal Master Mix II (Cat# 4440043, Applied Biosystems) and TaqMan™ Gene Expression Assays for MUC4 and GAPDH were (Assay ID: Hs00366414_m1; Cat# 4331182, and Assay ID: Hs03929097_g1; Cat# 4331182, Applied Biosystems, Foster City, USA). RQ-PCR reactions were performed as follows: one cycle at 95°C for 10 min, followed by 40 cycles at 95°C for 15 s and at 60°C for 1 min. Relative MUC4 expression level was calculated using $2^{-\Delta\Delta Ct}$ method [22].

IBM-SPSS version 20.0 software was used to analyse the data (IBM Corp, NY, US). Categorical data were expressed as frequencies and percentages. Shapiro–Wilk test was performed to determine the distribution for numerical data; normally distributed data were expressed as mean±SD while non-normally distributed data were described using median and interquartile range (25th and 75th percentile). For continuous variables, independent Student's t-test and Mann–Whitney's U test were used to compare the difference between the two groups. Chi-square analysis or Fisher exact test were carried out for categorical variables. The prognostic value of *MUC4* for OS and DFS of AML patients was estimated *via* Kaplan–Meier survival curves using log-rank test and Cox regression analysis. p-Value < 0.05 was considered significant.

Results

Baseline characteristics of the 70 AML patients are summarized in Table 1. Median (range) of the patient and controls were 33 (26–45 years) and 35 (29–50), respectively (p = 0.191). The number of men and women was 46/34 patients and 15/11 controls (p = 0.468). The majority of the patients were classified as acute myeloblastic leukaemia with maturation/acute myelomonocytic leukaemia (M2/M4) subtypes. *MUC4* expression level was significantly increased in AML bone marrow samples compared to healthy donors at median (range) 2.77 (0.7–16.6) and 1.14 (0.5–1.99) respectively (p = 0.005). Of the 70 patients, 45 (64%) achieved CR after the first induction, but 15 (33% of CR; 21% of total) relapsed later. Resistant and relapsed patients were collectively labelled as 'poor responders' (47.4%), while patients with persistent remission (52.6%) were labelled as 'good responders'.

Patients were assigned to two groups based on the median expression level of *MUC4*. Table 2 shows that *MUC4* expression level is significantly lower in patients with persistent remission, being alive or good responders. The level of *MUC4* expression is strongly associated with FAB subtypes, treatment response, survival status and final outcome. There were no links between *MUC4* expression and other clinical variables, including gender, age, white blood cells count, haemoglobin, platelet count, BM blasts, karyotypic classifications and FLT3 mutation.

During 41 months of follow-up, the mean (95% CI) OS and DFS intervals were 18.9 months (14.3–23.3) and 21.0 (16.8–25.1), respectively. Kaplan-Meier analysis highlighted that high *MUC4* expressers suffered from significantly worse OS (p = 0.011, Figure 1(a)) and shorter DFS (p = 0.006, Figure 1(b)) than low expressers.

In Cox proportional hazard model, univariate analysis showed that high bone marrow *MUC4* expression level was an independent prognostic indicator for predicting poorer OS and DFS (Table 3). In adjusting for age and sex, hazard ratios for OS and DFS were 2.9 (1.5–5.9) (p = 0.002), and 4.3 (1.4–13.9) (p = 0.014) respectively.

Table 1. Baseline characteristics of AML patients.

Variables		N (%)
Gender	Male	46 (65.7)
	Female	24 (34.3)
Age, median (range), years		33 (26–45)
FAB classification	M0	1 (1.4)
	M1	5 (7.1)
	M2	33 (47.1)
	M4	23 (32.9)
	M5	7 (10)
	M6	1 (1.4)
Organomegaly	Hepatomegaly (present *vs* absent)	12/58
	Splenomegaly (present *vs* absent)	11/59
	Lymphadenopathy (present *vs* absent)	21/49
FLT3 mutation	Wild	59 (84.3)
	Mutant	11 (15.7)
Karyotype classifications	Favourable	24 (34.3)
	Intermediate	33 (47.1)
	Adverse	13 (18.6)
Treatment response	Induction death	13 (18.6)
	Resistant	12 (17.1)
	Relapse	15 (21.4)
	Persistent remission	30 (42.9)
Survival status	Dead	39 (55.7)
	Alive	31 (44.3)
Final outcome	Poor (Resistant+ Relapse)	27 (47.4)
	Good (Persistent remission)	30 (52.6)

Categorical data are expressed as number (percentage). AML, acute myeloid leukaemia; FAB, French-American-British; M0, acute myeloblastic leukaemia with minimal differentiation; M1, acute myeloblastic leukaemia without maturation; M2, acute myeloblastic leukaemia with maturation; M4, acute myelomonocytic leukaemia; M5, acute monocytic leukaemia; M6, acute erythroid leukaemia

Table 2. Link between clinical features of AML patients with aberrant expressed *MUC4*.

	MUC4 expression		
Variables	Low (n = 35)	High (n = 35)	*P*-value
Sex, male/female	21/14	25/10	0.314
Age (years)	34.3 ± 9.4	36.5 ± 11.3	0.386
WBC, $\times 10^9$/L	27.0 (4–98)	14.8 (5–62)	0.707
Hb, g/L	77 ± 17	80 ± 21	0.466
PLT, $\times 10^9$/L	29 (13–62)	31 (18–57)	0.617
BM blasts, %	64.8 ± 22.5	56.1 ± 22.1	0.109
FAB classifications			**0.021**
M0	0 (0%)	1 (2.9%)	
M1	4 (11.4%)	1 (2.9%)	
M2	12 (34.4%)	21 (60%)	
M4	12 (34.3%)	11 (31.4%)	
M5	7 (20%)	0(0%)	
M6	0 (0%)	1 (2.9%)	
FLT3 mutation			0.324
Wild	28 (80%)	31 (88.6%)	
Mutant	7 (20%)	4 (11.4%)	
Karyotype classification			0.216
Favourable	9 (25.7%)	15 (42.9%)	
Intermediate	20 (57.1%)	13 (37.1%)	
Adverse	6 (17.1%)	7 (20%)	
Treatment response			0.001
Induction death	6 (17.1%)	7 (20%)	
Resistant	2 (5.7%)	10 (28.6%)	
Relapse	4 (11.4%)	11 (31.4%)	
Persistent remission	23 (65.7%)	7 (20%)	
Survival status			0.002
Dead	13 (37.1%)	26 (74.3%)	
Alive	22 (62.9%)	9 (25.7%)	
Final outcome			<0.001
Poor	6 (20.7%)	21 (75%)	
Good	23 (79.3%)	7 (25%)	

Data are expressed as mean±SD, median (interquartile range) and frequency (percentage) categorical data. AML, acute myeloid leukaemia; WBC, White blood cells; HB, haemoglobin; PLT, platelet, BM, bone marrow; FAB, French-American-British; M0, acute myeloblastic leukaemia with minimal differentiation; M1, acute myeloblastic leukaemia without maturation; M2, acute myeloblastic leukaemia with maturation; M4, acute myelomonocytic leukaemia; M5, acute monocytic leukaemia; M6, acute erythroid leukaemia

Discussion

Despite numerous studies on the oncogenic potential of *MUC4* in different malignancies, there is no detailed study on the expression of *MUC4* in AML. Thus, we explored the *MUC4* expression level in order to evaluate for the first time its clinical significance as a potential prognostic tool for adult AML. The bone marrow expression level of *MUC4* was significantly elevated in AML compared to the control group. Additionally, the high *MUC4* expression level was associated with worse survival and shorter DFS. Finally, *MUC4* expression level was found to be an independent predictor for AML.

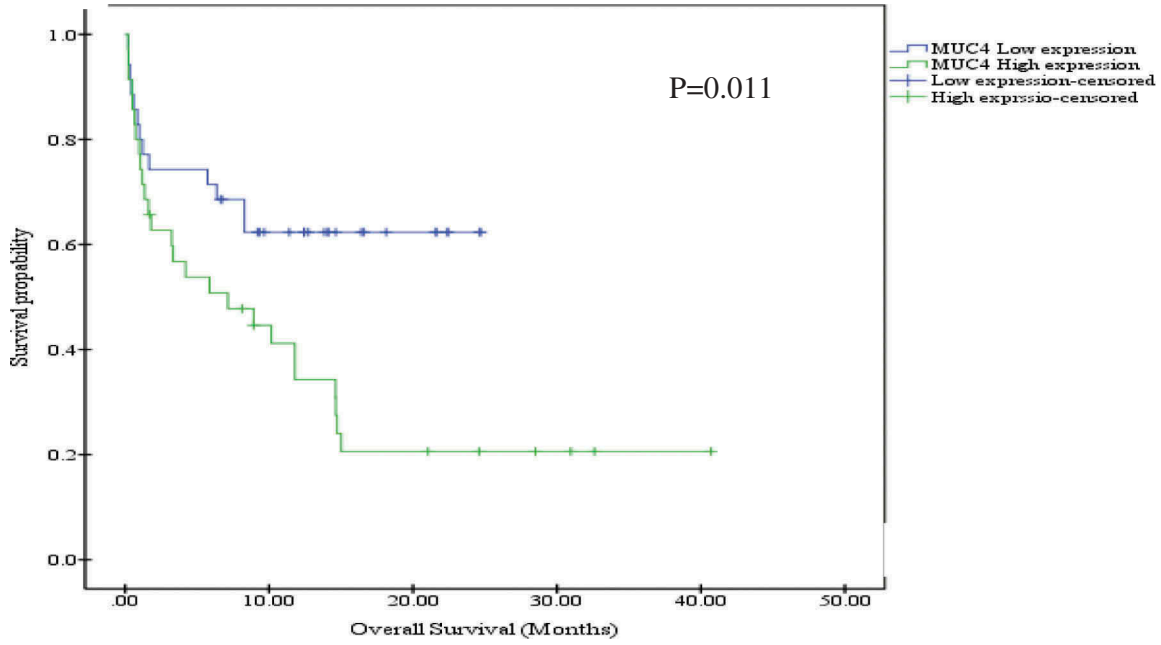
Several researches have supported a role for MUC4 in various cancers, where it is involved in cellular functions as tumour growth, proliferation, adhesion, invasion, inhibition of apoptosis, and chemo-resistance [23]. However, there is contradictory data about its expression level; Sadras et al. reported that *MUC4* expression was up-regulated in Ph-like CRLF2-rearranged acute lymphoblastic leukaemia compared to non- Ph-like CRLF2-rearranged acute lymphoblastic leukaemia group [24]. In addition, MUC4 over-expression was found in lung adenocarcinoma [17], ovarian cancer [18], breast cancer [13], pancreatic cancer [14], and mucoepidermoid carcinomas of the salivary gland [19]. This is supported by the results of the current work. In contrast, a reduced *MUC4* expression was exhibited in prostatic adenocarcinoma tissues compared to the adjacent benign tissue [15]. Additionally, the expression of MUC4 is lower in urothelial carcinoma [16].

This aberrant over-expression may be attributed to different mechanisms. Firstly, an association between alterations of *MUC4* copy number and *MUC4* expression was found [25]; therefore, amplification of the *MUC4* locus may contribute to this over-expression.

Secondly, regulators such as growth factors, cytokines, and miRNA may affect the alteration of *MUC4* expression [26–29]. Mejías-Luque et al. demonstrated that IL-6 is responsible for *MUC4* up-regulation in gastric cancer cell lines through the STAT pathway [30]. In addition, Stevens et al. showed that IL-6 activates STAT3 signalling in paediatric AML [31]. Further, bone marrow and plasma IL-6 levels are elevated in AML and this elevation correlates with shorter survival [32,33]. Collectively, we suggest that *MUC4* over-expression might be mediated *via* IL-6 induced STAT3 activity. This is speculative and further molecular mechanisms should be involved.

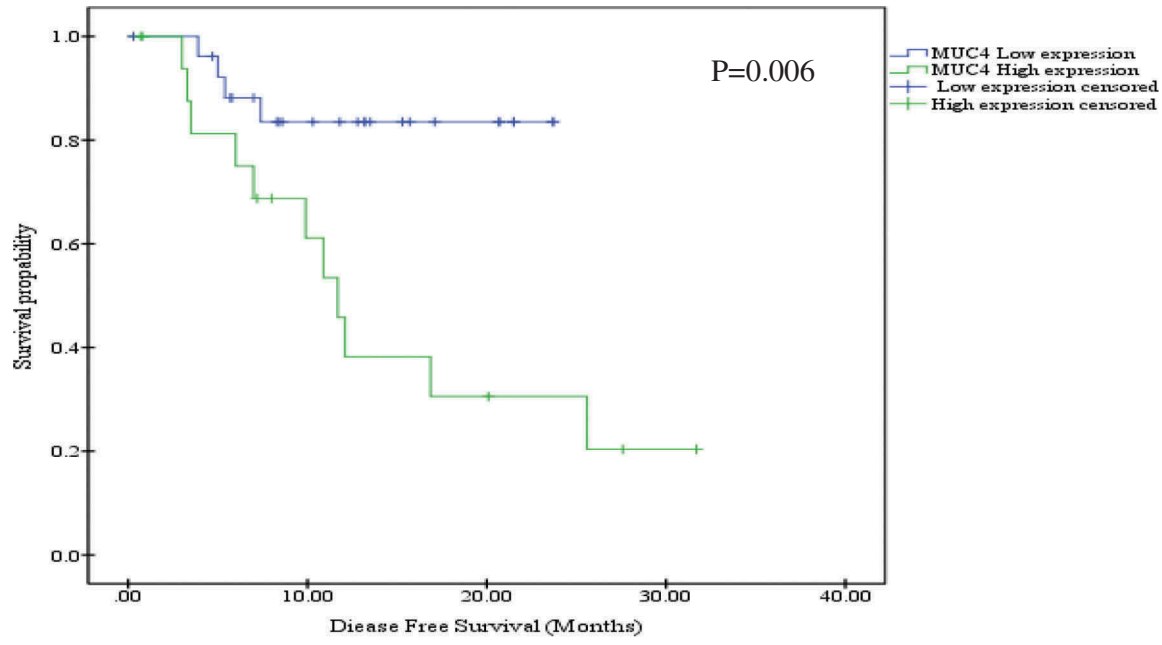
Although MUC4 is considered as a prognostic marker in various cancers, its exact potential in AML is still blurred. We found that *MUC4* over-expression

a)



Expression	Total N	N of events	N of censored
Low	35	13	22
High	35	26	9
Overall	70	39	31

b)



Expression	Total N	N of events	N of censored
Low	27	4	23
High	18	11	7
Overall	45	15	30

Figure 1. Kaplan–Meier survival curves: (a) overall survival and (b) disease-free survival according to *MUC4* expression.

Table 3. Univariate analysis for overall survival and disease-free survival.

	Univariate analysis	
Variables	HR (95% CI)	*P*-value
Overall survival		
MUC4	2.3 (1.2–4.5)	0.014
Sex	1.2 (0.6–2.2)	0.650
Age (years)	0.9 (0.5–1.7)	0.730
FAB classifications	1 (0.8–1.3)	0.950
FLT3 mutation	0.6 (0.2–1.6)	0.311
Karyotype classification	1.0 (0.7–1.6)	0.834
Disease-free survival		
MUC4	4.4 (1.4–14.2)	0.012
Sex	1.1 (0.4–3.1)	0.881
Age (years)	1.5 (0.5–4.1)	0.485
FAB classifications	0.7 (0.5–1.1)	0.131
FLT3 mutation	0.7 (0.2–2.6)	0.638
Karyotype classification	1.2 (0.6–2.4)	0.589

AML, acute myeloid leukaemia; FAB, French-American-British; HR, hazard ratio; 95% CI: 95% confidence interval.

predicted a poorer OS and shorter DFS of AML patients. Moreover, multivariate Cox analysis highlighted the clinical significance of *MUC4* levels for the AML prognosis independently of patients' clinicopathological data. Notably, Rakha et al. highlighted that the up-regulated levels of MUC4 in breast cancer patients are associated with worse overall survival [34]. Moreover, increased MUC4 expression was associated with a decreased survival rate among patients with cholangiocarcinoma and with colorectal adenocarcinoma [35,36]. Additionally, MUC4 is over-expressed in biliary tract cancer and this increase is associated with poor survival rate [37]. Conversely, MUC4 over-expression is associated with improved patient survival and prolonged time to relapse in mucoepidermoid carcinoma of salivary glands [19].

MUC4 has been implicated in suppression of apoptosis and stimulation of proliferation in several cancers; Workman et al. demonstrated that MUC4 over-expression suppressed apoptosis through augmentation of ErbB2/HER2 signalling to regulate anti-apoptotic Bcl-2 proteins in breast cancer cells [38]. Further, Skrypek et al. revealed that gemcitabine efficacy was improved in *MUC4* knockdown pancreatic cancer cell lines. The authors showed this knockdown decreased the activation of the mitogen-activated protein kinases (MAPK), c-Jun-NH2-kinase (JNK), and nuclear factor-kappa beta (NF-κB) pathways [39]. In ovarian cancer cells, *MUC4* over-expression induced the phosphorylation of focal adhesion kinase (FAK), a non-receptor tyrosine kinase, and the activation of Akt and extracellular signal-regulated kinase (ERK) pathways [40]. These events can promote cell migration and proliferative responses that may contribute to the severity of the disease and in turn a worse OS.

Due to the limited number of cases in our study, further studies are needed using a larger sample size to determine the mechanism of aberrant *MUC4* over-expression and to elucidate the molecular pathway linking MUC4 to leukaemic progression and resistance to therapy. Nevertheless, our data offers convincing evidence that bone marrow *MUC4* expression is markedly elevated in AML and is closely associated with poor clinical outcome. Therefore, bone marrow *MUC4* might serve as a novel prognostic biomarker for AML and may provide a new target for therapy.

This work represents an advance in biomedical science because it links *MUC4* expression level with prognosis in AML.

Summary table

What is known about this topic:
- In solid malignancies, MUC4 expression is associated with chemoresistance.
- MUC4 expression may induce invasion and metastasis in various types of cancer.

What this work adds:
- Increased levels of *MUC4* gene expression in *de novo* AML patients compared to healthy controls.
- *MUC4* gene level acts as a novel prognostic marker in AML.

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Disclosure statement

The authors declare no conflict of interest.

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