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# Interrogating Gender Influence on the Prognosis of Acute Myeloid Leukaemia (AML)

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**Abstract** Acute myeloid leukaemia (AML) is a complex haematological malignancy characterised by a clonal expansion of the myeloid progenitor. Factors such as molecular/cytogenetic abnormalities influence the prognosis of this condition. However, gender predominance in AML and how it influences the outcome of the condition has not been studied. Raw data of 20,000 gene expressions in 180 AML patients were retrospectively retrieved from the Cancer Genome Atlas Genomic Data Commons portal. A linear model was fitted to calculate the impact of each gene on the overall survival. The coefficient value was set to 2, and a P value of < 0.01 was set to denote significance. Almost twice as many male patients were at poor cytogenetic risk than females regardless of their vital status. Male-abundant genes were highly expressed in patients with poor prognosis. However, none of these genes correlated with previously reported genes, such as FLT3. It was noted that many of the highly expressed genes in patients with poor prognosis were dominant in male patients. The lack of correlation between these genes and previously established genes indicate that male patients are at a higher risk of developing more severe forms of AML and carry a poorer prognosis than females.

***Keywords:*** *AML, gender, genetics, prognosis*

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## 1. Introduction

Acute myeloid leukaemia (AML) is a haematological malignancy characterised by a clonal expansion of the haematological myeloid progenitor in blood and bone marrow. The development of the current understanding of AML pathophysiology and molecular interactions involved in this condition has changed it from an incurable condition to a curable one. It is estimated that slightly over 35% of treated patients under 60 years of age are being cured with the current standard line of therapy [1,2]. AML is a heterogeneous disease in which diseased cells vary in size and phenotype, and therefore, bone marrow biopsy and aspirate are key to diagnosis [3].

In efforts to dissect the heterogeneity of AML, the World Health Organization (WHO) classification came into effect in 2008, replacing the old French-American-British classification [4]. The European LeukemiaNet (ELN) has classified patients with AML into four prognostic categories based on a set of previously described cytogenetics and molecular abnormalities that influence overall survival and disease-free survival [5,6]. Age is an independent prognostic factor which correlates inversely with overall survival due to accumulating alterations and mutations as well as the ability of older patients to withstand more aggressive treatment regiments [7].

Gender predominance in AML and how it influences the outcome of the condition have not been addressed in previous studies. In this retrospective study, critical molecular signatures, namely DNA gene microarray, were used to describe the gender differences in AML and how they impact the disease prognosis and patient survival.

## 2. Methods

Raw gene expression data were retrieved from the Cancer Genome Atlas (TCGA) through the Genomic Data Commons portal [8]. The used data were from the American Acute Myeloid Leukemia Project under the project ID 'TCGA-LAML' [9].

After the retrieval of gene expression data for this study, data were analysed retrospectively using R along with a set of specialised packages ('gplots', 'survival', 'limma') [10].

In order to correlate between the different sets of genes across the whole patient cohort, the Shapiro-Wilk test was applied to assess the normalisation of these data (parametric vs nonparametric), and single correlation tests were applied using the Pearson correlation method. Overall survival was calculated based on the number of

days from the initial visit to the last visit within the study period, and the vital status of the patients (living or deceased), which were provided in the clinical data of the cohort. A linear model was fitted to calculate the impact of each gene on the overall survival, with the coefficient value set to 2 and a P value of < 0.01 set to denote significance.

This study was approved by Taibah University, College of Medicine Research Ethics Committee and registered with the study ID: 028-1441.

# 3. Results

## 3.1. Patients Characterisations

Patients included in this study were predominantly male (109 males vs 91 females) and were diagnosed with AML at a median of 57.5 years old (ranging between 18 and 88 years old; Table 1).

**Table 1. Characteristics of the studied cohort based on gender**

| | Male | Female |
|---|---|---|
| Number of patients | 109 | 91 |
| % of the total study cohort | 54.5% | 45.5% |
| Age | 57.5 (18–88) | 46.9 (22–79) |
| Number of live patients* | 39 | 36 |
| Number of deceased patients* | 70 | 51 |
| % of deceased patients* | 64.2% | 56% |

Notes: The table shows the number of participants in this project with their median age and range between brackets. *At the time of data collection.

Patients were categorised into three cytogenetic risk groups based on their cytogenetic make-up: favourable (n = 38), intermediate (n = 106) and poor (n = 44). Interestingly, the number of male patients with poor cytogenetic risk were almost twice as high as that of females regardless of their vital status (deceased: 22 males and 13 females; living: 6 males and 3 females; Table 2). Almost two-thirds of the subjects (n = 121) were deceased at the time of the study, 70 of which were males (Table 2).

**Table 2. Gender-distributed patient categorisation based on cytogenetic risk**

| | Deceased | | Living | |
|---|---|---|---|---|
| Cytogenetic risk | Male | Female | Male | Female |
| Favourable | 6 | 8 | 14 | 10 |
| Intermediate | 42 | 30 | 19 | 15 |
| Poor | 22 | 13 | 6 | 3 |

Note: The table contains the patients' distribution based on their vital status, gender and cytogenetic risk.

## 3.2. AML Gender-specific Genetic Signature

TCGA gene expression data included over 20,000 gene expressions for 180 subjects. Genes were then compared based on their abundance in either males or females.

An array of genes, including DDX3Y and KDM5D, were highly expressed in males, whereas XIST and its antisense gene TSIX were expressed highly in females (Figure 1).

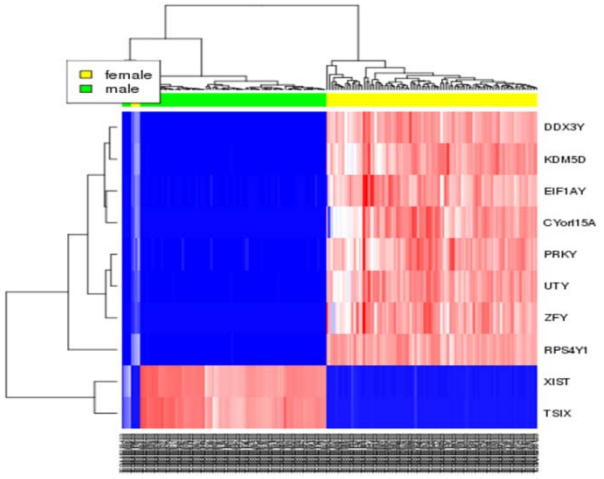


**Figure 1.** Heatmap of the gender-specific gene expression in AML patients. The first eight genes were exclusively expressed in males, whereas XIST and TSIX were expressed in females. Yellow denotes female and green denotes male subjects. The heatmap is on the blue-red scale (blue: high expression; red: low expression).

These eight male-predominant genes were expressed on the Y chromosome, whereas XIST and TSIX were expressed on the X chromosome.

## 3.3. Novel Genes Which Are Highly Expressed in AML Patients with Poor Cytogenetic Risk

The next objective was to identify which genes are highly expressed in patients with poor prognosis and to assess whether any of the reported genes would be included in this cohort. The IL7 gene came at the top of the highly expressed genes in AML (Table 3).

**Table 3. List of genes that are highly expressed in AML patients with poor cytogenetic prognosis**

| Gene | logFC | Ave Expr | t | P.Value | B | Location |
|---|---|---|---|---|---|---|
| *CPNE8* | -2.91 | 2.79 | -11.49 | 3.16E-23 | 1.89 | chY |
| *HOXA9* | -4.24 | 4.07 | -11.40 | 5.98E-23 | 1.27 | chY |
| *RMND5B* | -1.13 | 2.87 | -11.10 | 4.32E-22 | 9.36 | chX |
| *SIX3* | 2.21 | 0.55 | 10.98 | 9.50E-22 | 8.60 | chY |
| *LPO* | 3.08 | 2.63 | 10.82 | 2.64E-21 | 7.61 | chX |
| *PDE4DIP* | -1.08 | 2.27 | -10.78 | 3.58E-21 | 7.32 | chY |

Note: Note: The table demonstrates the top six highly expressed genes in patients with poor cytogenetic risk and lists their average expression, t testing across the cohort and P value.

This overexpression was surprising, as the IL7 gene is a critical gene for lymphoid development, particularly T cells. None of the genes that were reported to be of high impact on the prognostic value, such as Fms-Like Tyrosine Kinase 3 (FLT3) (11), Nucleophosmin 1 (NPM1) or TET2 (3), were identified in this group. These genes were not expressed differentially in the favourable cytogenetic risk group either. Interestingly, six of the eight highest expressed genes in AML patients with poor prognosis were located on the Y chromosome.

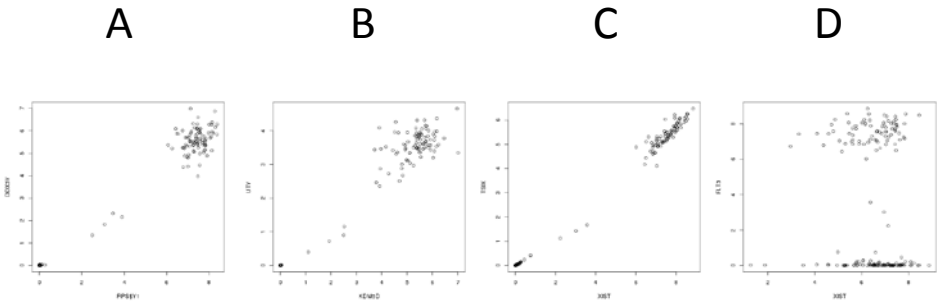


**Figure 2.** Plots of gender-dominant genes with their correlations. Plots show the correlation of male-abundant genes: (A) DDX3Y and RPS4Y1, and (B) KDM5D and UTY. (C) The female-dominant XIST correlates with TSIX, and (D) demonstrates the independent expression of FLT3

### 3.4. Gender-specific Genes do not Correlate with Previously Reported Genes

Next was to examine whether these male-abundant genes correlate with each other in AML patients and to see if they correlate with the previously reported significant genes. Male-abundant genes correlated highly with each other (P value < 2.2e-16) (Figure 2), as did XIST with its antisense gene TSIX. Interestingly, none of these genes correlated with the previously reported genes.

## 4. Discussion

AML is a very complex disease in which many factors could contribute to the prognosis and overall survival of the disease. Apart from age, which is considered to be an independent prognostic factor in AML [7], several molecular abnormalities have been described as carrying a prognostic value [3]. As far as the current study is concerned, gender has not been previously ascribed prognostic significance. In this cohort, however, gender was determined to carry prognostic value. Most of the patients with poor or unfavourable cytogenetic prognosis were males. Also, the majority of the deceased patients in this cohort were males, suggesting the male gender to be a poorer prognostic factor. These findings are in line with similar findings in different cohorts of larger size and at different time intervals [12,13,14]. Interestingly, many of the highly expressed genes in patients with unfavourable cytogenetic profile did not correlate with genes, such as FLT3 and NPM1, that were previously associated with the unfavourable prognosis [15,16].

Male abundance in AML, in particular in patients with lower overall survival and unfavourable prognosis, can be observed in previous studies [17]. Yazarloo and colleagues found that the expression of several genes linked to testicular cancer was differentially expressed in male AML patients [18]. These findings further support that the male gender carries a poorer prognosis than the female gender.

As gender was not considered to be a prognostic factor in any of these studies, nor was it linked to any cytogenetic or molecular features of AML, this study is the first of its kind in AML. The use of gender as an independent prognostic factor was previously determined in other haematological malignancies, such as acute lymphoblastic leukaemia and chronic myeloid leukaemia [19,20]. Furthermore, the male gender has also been determined as an independent predictor for worse survival and relapse in a large consecutive cohort of elderly with diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone [21]. Yet, these studies could not determine the cellular or molecular differences giving rise to such prognostic difference between males and females.

The novel finding of the overexpression of the IL7 gene in this cohort of patients could be of functional significance. Wendelbo and colleagues found that patients with untreated AML suffer from a reduced systemic IL-7 [22], which was corrected upon response to therapy. Taken together, IL-7 overexpression could be a physiological response to compensate for the lack of IL-7 or highlight a novel abnormality in AML in which IL-7 translation is potentially impaired.

Similar to this study, HOXA9 gene overexpression with its leukaemogenic potential was reported to be one of the most correlating factors to poor prognosis for human AML [23,24]. In this study, the HOXA9 gene was also the second-most expressed gene among patients who were classified with poor prognosis.

Limitations of this study include the following:

1- This study does not exhaust every possible molecular mechanism that might contradict these findings, such as DNA methylation or RNA sequencing.
2- The cohort in this study might not be representative, as many of the previously reported genes that had an impact on the prognosis and the overall survival were not of significance in this cohort.

### 4.1. Conclusion

In conclusion, the results of this study suggest that the male population is at higher risk of developing more severe forms of AML and, thus, carry a poorer prognosis compared to females. This was demonstrated in the higher male proportion with poor unfavourable prognosis as well as those who were deceased.

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