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# Role of tissue inhibitor of matrix metalloproteinase-1 in Iraqi patients with acute myeloid leukemia

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**Abstract:**

**BACKGROUND:** Leukemia is characterized by an uncontrolled expansion or proliferation of hematopoietic cells that are unable to develop appropriately into mature blood cells. Tissue inhibitor of metalloproteinases (TIMP) is glycoprotein with 28 Da Molecular weight. It has proteolytic and proliferative activity show pleiotropic effects in the bone marrow regulates cell responsible for survival and growth also healthy hematopoietic progenitor cells and involve in cancer progression.

**OBJECTIVES:** The aim of this study was to measure TIMP in Iraqi acute myeloid leukemia patients as well as the correlation between tissue inhibitor of matrix metalloproteinase-1 and blast cells.

**PATIENTS MATERIALS AND METHODS:** The study involved 50 patients from Iraqi National Hematology Center/Al-Mustansiriyah University and Baghdad Teaching Hospital with acute myeloid leukemia and 50 control participants who were physically similar. The patients' ages ranged from 20 to 70 years. Tissue inhibitor of matrix metalloproteinase concentration in plasma was measured using a sandwich enzyme immunoassay approach that is quantitative.

**RESULTS:** The present study demonstrates a statistically significant increase in the level of tissue inhibitor of matrix metalloproteinase-1 patients with acute myeloid leukemia. The level of TIMP-1 in serum AML patients was 443.7 ± 0.3 pg/mL while in healthy control serum was 149.5 ± 0.088 pg/mL. The current result showed a positive significant correlation between TIMP-1 level and blast Cells percentage ($r$ = 0.495; $P$ = 0.031), while the correlation between leukocytes number and platelets number was insignificant ($r$ = 0.388; $P$ = 0.078, $r$ = –0.444; $P$ = 0.155).

**CONCLUSION:** TIMP-1 levels increased in the CML patient compared with healthy control also there was a significant correlation between TIMP-1 and Blast cell level while no correlation between level of TIMP-1 and number of leukocytes and platelets. The level of TIMP in patients untreated and undergoing chemotherapy does not change.

**Keywords:**

Acute myeloid leukemia, bone marrow, tissue inhibitor of matrix metalloproteinase

## Introduction

Leukemia is characterized by an uncontrolled expansion or proliferation of hematopoietic cells that are unable to develop appropriately into mature blood cells.[1] Acute myeloid leukemia (AML) is a disease with great morphological and genetic heterogeneity or disorder which originates from a rare inhabitance of leukemia stem cells.[2]

Tissue inhibitor of metalloproteinases (TIMP) is glycoprotein with 28 Da Molecular weight.[3] It has proteolytic and proliferative activity show pleiotropic effects in the bone marrow regulates cell responsible for survival and growth also healthy hematopoietic progenitor cells and involve in cancer progression.[4] It has been shown that matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) have considerably greater effects on the development and invasiveness of numerous

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malignant illnesses. TIMP has a family of four kinds: TIMP-1, TIMP-2, TIMP-3, and TIMP-4. TIMPs have the capacity to obstruct all known MMP actions by creating noncovalent interactions with the MMPs. TIMP-1 and TIMP-2 are multipurpose proteins that have a variety of effects that prevent angiogenesis.[5] TIMP-1 encourages lymphoma cell proliferation, and elevated TIMP-1 serum levels are linked to a bad prognosis in a number of malignancies.[6] TIMP-3 might possess a variety of anticancer traits, such as the ability to induce apoptosis, and has antiproliferative, antiangiogenic, and antimetastatic actions.[7] The expression levels of TIMPs in AML patients can have prognostic implications. In many solid cancers, including breast and prostate carcinoma, TIMP-1 overexpression is linked to poor prognosis and early recurrence.[8,9] High levels of TIMP-1, for example, have been associated with a poorer prognosis in some cases, while others have shown the opposite correlation. The serum levels of tissue inhibitors of metalloproteinases-1 were much higher in patients who underwent intense treatment for acute myeloid leukemia.[10] The objective of this study was to determine the prognostic significance of TIMP-1 levels in patients who had chemotherapy with acute myeloid leukemia. Some studies have reported elevated levels of TIMP-1 in the blood or BM of AML patients. Elevated TIMP-1 levels may be associated with a more aggressive form of AML or a poorer prognosis in some cases. Conversely, there are also reports of decreased TIMP-1 levels in AML patients. Reduced TIMP-1 levels may be associated with specific AML subtypes or could be related to the stage of the disease.

TIMP-1 levels have been linked to therapy responsiveness in AML, according to some studies. TIMP-1 levels that are high may be associated with resistance to particular medications.

## Patients Materials and Methods

The study involved 50 patients from Iraq with acute myeloid leukemia and 50 control participants who were physically similar. The patients' ages ranged from 20 to 70 years. The current study was conducted at the National Center of Hematology, Al-Mustansiriyah University, from January 2021 to June 2023. Each patient underwent a physical examination by a professional clinical hematologist, and data on illnesses relevant to this study were gathered and also complete blood picture (CBC) was obtained from each patient. The inclusion criteria include the following: newly diagnosed AML patients with a period of more than 1 year, AML patients with treatment of chemotherapy, the age group of patients above 20 years, and AML patients including all stages of the disease, while the exclusion criteria include AML < 20 years.

Tissue inhibitor of matrix metalloproteinase concentration in plasma was measured using a sandwich enzyme immunoassay approach that is quantitative (ELISA) using a kit from (R and D Systems, USA).

Ethical approval: The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and it was approved by a review ethical committee with approval reference 2/2021. Written informed consent was obtained from every patient before the start of the study.

### Statistical analysis

Discrete variables are analyzed for the mean, standard deviation, and person correlation. The categorical variables are analyzed using SPSS version 28. A value of $P < 0.01$ was considered statistically significant.

## Results

Fifty acute myeloid leukemia patients were investigated. There were 23 out of 50 (46%) patients with an age group ≥50 years and 27 out of 50 (54%) patients with an age group <50 years. The age's mean of AML patients was 46.25 ± 2.87 years and control mean age was 45.79 ± 1.44 years. The patients and healthy control divided in to two groups according to gender. Since there were 29 more male patients with AML than female patients (M: F), or 58% versus 42%, there was a prevalence of the male gender among our patients.

The level of tissue inhibitor of matrix metalloproteinase-1 in AML patient serum was 443.7 ± 0.3 pg/mL, while the concentration of tissue inhibitor of matrix metalloproteinase-1 of the healthy control serum was 149.5 ± 0.088 pg/mL.

The present study demonstrates a statistically significant increase in the level of tissue inhibitor of matrix metalloproteinase-1 patients with acute myeloid leukemia as compared with control subjects ($P < 0.01$), as listed in Table 1. Conversely, we did not observe a statistically significant distinction between TIMP-1 levels in patients before and after undergoing chemotherapy ($P = 0.9$) [Table 2].

The current result showed a positive significant correlation between TIMP-1 level and blast Cells number ($r = 0.495$; $P = 0.031$), while the correlation between leukocytes number and platelets number was insignificant ($r = 0.388$; $P = 0.078$, $r = -0.444$; $P = 0.155$) [Table 3].

## Discussion

Acute myeloid leukemia (AML) is an exceptionally aggressive hematologic malignancy marked by the buildup of immature myeloid cells within the

**Table 1: Tissue inhibitor of matrix metalloproteinase-1 level among patients and controls**

| TIMP-1 (pg/mL) | *n* | Mean±SD | *P* | *t*-test |
|---|---|---|---|---|
| Patients | 50 | 443.7±0.3 | 0.0089 | 3.9* |
| Controls | 50 | 149.5±0.088 | | |

*$P$<0.01. SD=Standard deviation, TIMP=Tissue inhibitor of metalloproteinases

**Table 2: Comparison between acute myelogenous leukemia patients before and after chemotherapy**

| TIMP-1 (ng/mL) | *n* | Mean±SD | *P* | *t*-test |
|---|---|---|---|---|
| Before therapy | 25 | 11.10±0.95 | 0.9 | −0.1 |
| After therapy | 25 | 11.13±0.67 | | |

TIMP=Tissue inhibitor of metalloproteinases, SD=Standard deviation

**Table 3: Correlation among tissue inhibitor of matrix metalloproteinase-1, leukocytes, blasts, and platelets in new diagnosis patients**

| Correlations | | | |
|---|---|---|---|
| TIMP-1 | Blast cells | Leukocytes | Platelets |
| Pearson correlation | 0.495* | 0.388 | −0.444 |
| Significant (two-tailed) | 0.031 | 0.078 | 0.155 |
| *n* | 50 | 50 | 50 |

*Correlation is significant at the 0.05 level (two-tailed). TIMP=Tissue inhibitor of metalloproteinases

BM, leading to the disruption of regular blood cell production. Regrettably, AML exhibits a dismal prognosis, characterized by a notable disease relapse rate and a median overall survival of merely 15 months. Troublingly, the standard therapeutic approaches for AML have seen limited progress over the past three decades, underscoring the substantial difficulties associated with advancing treatment strategies within the current scope of research.[11] TIMPs are involved in both pathogenic and various normal activities, including tumor invasion and metastasis. Matrix metalloprotease MMPs and TIMPs are implicated in the development and spread of lymphoid neoplasia, according to a wealth of evidence.[12] The present study showed elevate in concentration of TIMP in patients with AML these results were agreed previous study.[4] Elevated TIMP-1 levels have been linked to a poor prognosis in some studies,[12,13] suggesting a potential function in predicting disease outcomes. TIMP-1 levels have been examined as potential prognostic markers in a variety of malignancies, including leukemia. TIMP-1 levels can fluctuate depending on a number of circumstances, including the subtype of AML, the stage of the disease, and individual patient characteristics. However TIMP-1 level varying in value according to the study of patients' population also the genetic factor. Because AML is a complicated disease with various genetic and clinical aspects, it is critical to realize that the association between TIMP-1 levels and AML is not straightforward. TIMP-1's participation in AML may be influenced by a variety of circumstances, including specific genetic abnormalities in leukemia cells. In the current study, the TIMP-1 was assessed by ELISA technique in the blood samples. Using more sophisticated and sensitive assessments like genetic expression in BM samples could be more considerable. Moreover, cancer cells exposed to cytotoxic drugs and existing in a suspended state exhibited an increased capacity for adhesion. This alteration led to the overexpression of particular ligands and/or receptors, ultimately playing a role in the emergence of drug resistance.[14,15]

## Conclusion

Our findings indicate that the levels of TIMP-1 exhibit significant elevation in AML patients. Notably, we observed that there is a correlation between TIMP-1 levels and development of disease. TIMP-1's participation in AML may be influenced by a variety of circumstances, including specific genetic abnormalities in leukemia cells. However, further investigation is still required.

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### Conflicts of interest
There are no conflicts of interest.

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