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# Evaluation of CD71 Expression in Acute Leukemia in Egyptian Patients

Authors
**Yasmin Nabil El-Sakhawy, Shaimaa Abdelmalik Pessar, Noha Hussein Boshnak**
Ain Shams University Egypt
Corresponding Author
**Yasmin Nabil El-Sakhawy**
Email: *yasminnabil@hotmail.com*, Mobile: 1005276531

**Abstract**
**Background:** *CD71 or transferrin receptor is an integral membrane protein that mediates cellular iron uptake. It has been identified as a proliferation marker being expressed on many solid tumours as well as hematological neoplasms. Hence, CD 71 expression was assessed as a flow cytometric marker for leukemia and lymphoproliferative neoplasms. However, only few studies aimed to address its diagnostic and prognostic implications as well as its relation to clinical and laboratory markers. So, our study aimed at evaluation of the significance of CD71 (transferrin receptor 1, TfR-1) as a flow cytometric marker for the diagnosis of acute leukemia (AL).*
**Methods:** *Seventy two patients diagnosed as acute leukemia; fifty six acute myeloid leukemia (AML) and sixteen Precursor B acute lymphoblastic leukemia (pre B ALL) were enrolled in the study and assessed for CD71 expression on blast cells by flow cytometry.*
**Results:** *CD71expression was found to be significantly higher in acute myeloid leukemias than precursor B lymphoblastic leukemia (p:0.000) while median of MFI of CD71 was significantly higher in B lymphoblastic leukemia (p:0.016) than acute myeloid leukemia with the most remarkable expression was on poorly differentiated AML FAB subtypes.*
**Conclusion:** *CD71 may be useful for the differential diagnosis of precursor B-ALL from AML in addition it could be useful in the evaluation of differentiation stage in case of AML.*
**Key Words:** *CD71, Transferrin receptor, Acute Leukemia, Poorly differentiated AML, Precursor B ALL.*

## Introduction

Acute leukemias either lymphoblastic or myeloid represent heterogeneous groups of neoplastic disorders with high morbidity and mortality rates along with heterogeneity in survival and prognosis [1,2].

Flow cytometric immunophenotyping has important role in acute leukemia. It is mandatory for the diagnosis of all cases of ALL, minimally differentiated AML and mixed phenotype acute leukemia. Also, immunophenotyping pattern help guiding genetic studies specific for this phenotype. As aberrant expression is frequently encountered, a battery of antibodies is required for definitive characterization of blast lineage [3].

Despite advances in classification, management strategies and prognostic tools, Extensive research is still needed for better understanding of evolution of acute leukemia, improve stratification, and better outcome.

The transferrin receptor (CD71) is an integral membrane protein that mediates the uptake of

transferrin-iron complexes[4]. Two transferrin receptors have been cloned (TfR1 and TfR2); however, TfR1 is considered the major protein responsible for iron uptake owing to its higher affinity and expression pattern [5]. CD71 is a homodimeric glycoprotein containing 760 amino acids, which binds to diferric transferrin at the cell surface. This makes iron available for heme synthesis and for many metabolic processes necessary for cell growth and proliferation, including DNA synthesis, electron transport, nitrogen fixation and oxygen sensing [4,6].

The expression of transferrin receptor is widespread; hepatocytes, endocrine pancreas, placental syncytiotrophoblasts, myocytes, spermatocytes, basal keratinocytes and erythroid precursors [6]. The highest expression presents on early erythroid precursors through the interme-diate normoblast phase, after which expression decreases through the reticulocyte phase [7-9].

CD71 overexpression has been reported in many neoplasms, including solid tumors such as lung [10,11], bladder [12], colon [13], pancreas [14] and breast cancer [15,16], gliomas[17] as well as hematological malignancies [18-20].

Higher expression of CD71 has been identified as a negative prognostic marker for numerous solid tumor types [14,16] as well as for non-Hodgkin's lymphoma [21-24]. The high consumption of iron by the proliferating cells to act as co-factor for ribonucleotide reductase which is necessary for DNA synthesis makes the basis of targeting CD71 as an experimental anticancer therapy [25].

There is still very little information on the poss-ible importance of CD71 in acute leukemias, and the data that is available is conflicting [22, 26, 27].

Our aim from this study is to evaluate the significance of CD71 (transferrin receptor 1, TfR-1) as a flow cytometric marker for the diagnosis of acute leukemia (AL).

**Subjects and Methods**

This study conducted on 72 patients (40 males and 32 females and age range 1-74 years) newly diagnosed as acute leukemia based on their morphology following French-American-British classification and immunophenotype in central Hematology Lab, Ain Shams University Hospital after consent from them or their guardians to use their samples in this study. They were exposed to the following laboratory investigations:

- Complete history taking and thorough clinical examination with special account on pallor, purpura, organomegaly and lymphadenopathy.
- 2 ml on $K_2$EDTA tube for complete blood count including differential white blood cells count on a Sysmex XE 2100 analyser with Leishman stained peripheral blood smear.
- *Bone marrow aspiration:*
  - Morphologic assessment and blast count.
  - Myeloperoxidase stain.
  - Immunophenotyping using our routine panel for acute leukemia and with measurement of CD71 expression on multiparameter flow cytometry (Coulter Epics XL flow cytometry, Coulter Corporation, Miami, FL, USA) using monoclonal Abs of Becton Dickinson Biosciences (BD Biosciences, San Jose, CA).

Fresh bone marrow cells were prepared by red blood cell lysing solution, and incubated with Flourochrome conjugated monoclonal antibodies at the concentrations recommended by the manufacturer. The antibody combinations used are listed below:

1) CD45, CD34, FITC Neg/PE Neg control 1.
2) CD45, CD34, CD15, CD117.
3) CD45, CD34, CD7, CD33.
4) CD45, CD34, HLA-DR, CD13.
5) CD45, CD34, CD14, CD64.
6) CD45, CD34, FITC Neg/PE Neg control 2.
7) CD45, CD34, CD2,CD19.
8) CD45, CD34, CD20,CD10.
9) CD45, CD34, CD38, CD56.
10) CD45, CD34, HLA-DR, CD71.
11) CD45, CD34, cytTdT, cytCD79a.
12) CD45, CD34, cytMPO, cytCD3.

Positivity level was determined based on a flourochrome-conjugated isotypic Ig control.

A minimum of 100,000 cells were recorded per sample. Data were analyzed with C: XL ACL&089, Run time protocol. Threshold gating of bone marrow mononuclear cells (BMMNC) was assigned based on forward scatter (FSC) and side scatter (SSC) to exclude red blood cells, dead cells and cell debris. A CD45/SSC scatter gram allowed gating BMMNC to define cell subsets for further immunophenotyping.

The percentage of CD71+ve cells and the mean fluorescent intensity (MFI) of CD71 on the gated cell populations were determined in comparison to the isotype control.

*Statistical analysis:*

Data were collected and entered to the Statistical Package for Social Science (IBM SPSS) version 20. Qualitative data were presented as number and percentages while quantitative data were presented as mean, standard deviations, ranges, medians with interquartile ranges (IQR). The comparison between groups regarding qualitative data were done by using Chi-square test while comparison between two group with quantitative data and parametric distribution were done by using Independent t-test and with non parametric distribution were done by using Mann-Whitney test. Also comparison between more than two groups regarding quantitative data with non parametric distribution were done by using Kruskall-Wallis test. Spearman correlation coefficients were used to assess the correlation between two quantitative parameters in the same group. The confidence interval was set to 95% and p-value was considered non significant at the level of > 0.05 (NS), significant at the level of > 0.05 (S) and highly significant at the level of < 0.01 (HS).

**Results**

About 72 individuals recently diagnosed with acute leukemia were enrolled in the study with their median age 33.5 yrs, IQR (11.5-50) yrs and range (1-74) yrs, with male to female ratio 1.2/1.

Distribution of hematological parameters, blast count and CD71 expression is demonstrated in table 1.

**Table (1):** Distribution of hematological parameters, blast count and CD71 expression:

| | **Median (IQR)** | **Range** |
|---|---|---|
| CD71 | 45.7 (14.6 – 79.75) | 0.89 – 97.4 |
| MFI | 2.2 (1.6 – 5.8) | 1.1 – 29.1 |
| TLC | 19 (7.95 –51.85) | 1 – 216 |
| Hb | 7.75 (6.65 – 9) | 4.2 – 12.5 |
| Plt | 24 (13.5 – 56) | 7 – 192 |
| Blast count | 74.5 (57.5 – 83.5) | 20 – 97 |

CD71 was found to be heterogenously expressed in acute leukemia cases with median 45.7%, IQR: (14.6 – 79.75) and range (0.89 – 97.4). MFI of CD71 with median 2.2, IQR: (1.6 – 5.8), and range (1.1 – 29.1) (figure 1).

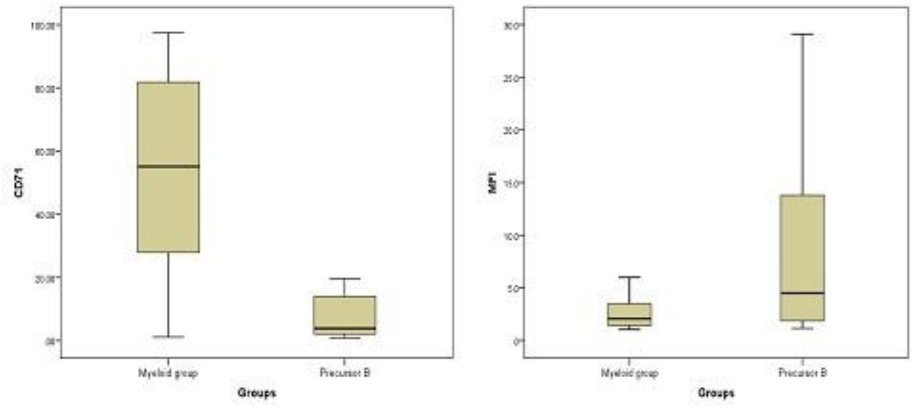


**Figure (1):** Median CD71 expression and MFI in both AML and pre B-ALL

Cases of acute leukemia comprised: 56/72 (77.8%) of cases were acute myeloid leukemia and 16/72 (22.2%) of cases were precursor B-acute lymphoblastic leukemia (table 2).

**Table (2):** The frequency of each leukemia type in our study:

| Type | No. | % |
|---|---|---|
| M0 | 1 | 1.4 |
| M1 | 9 | 12.5 |
| M2 | 14 | 19.4 |
| M3 | 8 | 11.1 |
| M4 | 10 | 13.9 |
| M5 | 9 | 12.5 |
| M7 | 5 | 6.9 |
| Precursor B | 16 | 22.2 |
| Total | 72 | 100 |

As expected, lymphadenopathy was significantly higher in Precursor B-ALL than in myeloid leukemia while hepatosplenomegaly showed no significant difference between myeloid and lymphoid leukemias (table 3).'

**Table (3):** Comparison between myeloid group and lymphoid group regarding organomegaly and LDN:

| | | Myeloid group | | Precursor B group | | Chi-square test | |
|---|---|---|---|---|---|---|---|
| | | No. | % | No. | % | $X^2$ | P-value |
| Liver | Negative | 25 | 44.6% | 6 | 37.5% | 0.259 | 0.611 |
| | Positive | 31 | 55.4% | 10 | 62.5% | | |
| Spleen | Negative | 23 | 41.1% | 4 | 25.0% | 1.371 | 0.242 |
| | Positive | 33 | 58.9% | 12 | 75.0% | | |
| LN | Negative | 35 | 62.5% | 5 | 31.2% | 4.922 | 0.027 |
| | Positive | 21 | 37.5% | 11 | 68.8% | | |

CD71expression was found to be significantly higher in acute myeloid leukemias than precursor B lymphoblastic leukemia (p:0.000) while median of MFI of CD71 was significantly higher in precursor B lymphoblastic leukemia than acute myeloid leukemia (0.016). Total leukocytic count was significantly higher in AML than pre B-ALL while blast count was significantly higher in pre B-ALL than AML. The percentage of blast cells in BM samples varied from 20 to 96 with Mean±SD 65.16 ± 19.02 in the AML group while in ALL was 42 to 97 with Mean±SD 80.94±14.5 (table 4).

**Table (4):** Comparison between myeloid and precursor B groups regarding the studied parameters:

| | | Myeloid group | Precursor B group | Mann-Whitney test | |
|---|---|---|---|---|---|
| | | Median (IQR) | Median (IQR) | Z | P-value |
| Age | Median (IQR)<br>Range | 37 (25.5 – 52)<br>1 – 74 | 8 (4 – 22.5)<br>1 – 64 | -3.198 | 0.001 |
| CD71 | Median (IQR)<br>Range | 55.1 (27.9 – 81.8)<br>1.12 – 97.4 | 3.87 (2.13 – 13.96)<br>0.89 – 87 | -4.558 | 0.000 |
| MFI | Median (IQR)<br>Range | 2.1 (1.5 – 3.5)<br>1.1 – 21 | 4.5 (1.9 – 13.8)<br>1.2 – 29.1 | -2.404 | 0.016 |
| | Range | 1 – 7 | 3 – 99 | | |
| TLC | Median (IQR)<br>Range | 20.5 (10.5 – 60.95)<br>1.2 – 216 | 10.2 (6.7 – 19.35)<br>1 – 108 | -2.195 | 0.028 |
| Hb | Mean±SD<br>Range | 8.02 ± 1.73<br>4.2 – 12.5 | 7.45 ± 1.76<br>4.8 – 12 | 1.163 | 0.249 |
| Plt | Median (IQR)<br>Range | 28 (18 – 65)<br>7 – 170 | 20.5 (10.5 – 42)<br>8 – 192 | 1.356 | 0.175 |
| Blast count | Mean±SD<br>Range | 65.16 ± 19.02<br>20 – 96 | 80.94±14.50<br>42 – 97 | 3.067 | 0.003 |

When correlating CD71 expression and MFI with age, immunophenotypic markers, hematological parameters and blast count: a significant positive correlation was found between CD71 expression and each of age, common myeloid markers; CD13, CD33,CD117 and a significant negative correlation with CD14 and HLA-DR and common lymphoid markers; CD10, CD19, CD20,

CD5. A significant negative correlation was found between mean fluorescence intensity of CD71 expression and each of age, TLC, CD13 and CD14 and a significant positive correlation with common lymphoid markers; CD10, CD19, CD20 (table 5 and figures 2&3).

**Table (5):** Correlation of CD71 and MFI with the studied parameters:

| | CD71 | | MFI | |
|---|---|---|---|---|
| | r | p-value | r | p-value |
| CD71 | | | 0.015 | 0.902 |
| MFI | 0.015 | 0.902 | | |
| Age | 0.360** | 0.002 | -0.228 | 0.054 |
| CD13 | 0.300* | 0.013 | -0.327** | 0.007 |
| CD33 | 0.243* | 0.048 | -0.231 | 0.061 |
| CD117 | 0.333** | 0.006 | -0.156 | 0.208 |
| CD14 | -0.281* | 0.021 | -0.274* | 0.025 |
| CD19 | -0.334** | 0.006 | 0.248* | 0.043 |
| CD20 | -0.247* | 0.044 | 0.322** | 0.008 |
| CD2 | -0.061 | 0.626 | -0.005 | 0.966 |
| CD5 | -0.260* | 0.033 | 0.149 | 0.229 |
| CD7 | -0.021 | 0.869 | -0.176 | 0.154 |
| CD34 | 0.040 | 0.750 | 0.114 | 0.357 |
| HLADR | -0.249* | 0.042 | -0.116 | 0.351 |
| CD10 | -0.391** | 0.001 | 0.259* | 0.034 |
| TLC | -0.108 | 0.368 | -0.517** | 0.000 |
| Hb | 0.083 | 0.489 | 0.000 | 0.997 |
| Plt | 0.103 | 0.390 | -0.087 | 0.466 |
| Blast count | -0.096 | 0.424 | 0.044 | 0.714 |

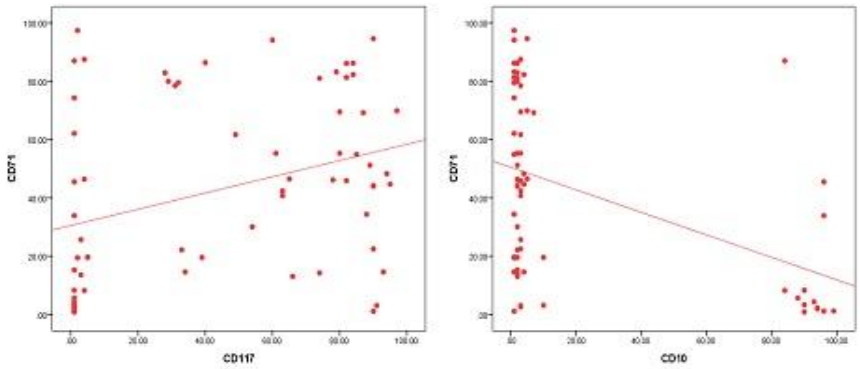


**Fig (2):** CD71 expression positively correlates with CD117 and negatively correlates with CD10.

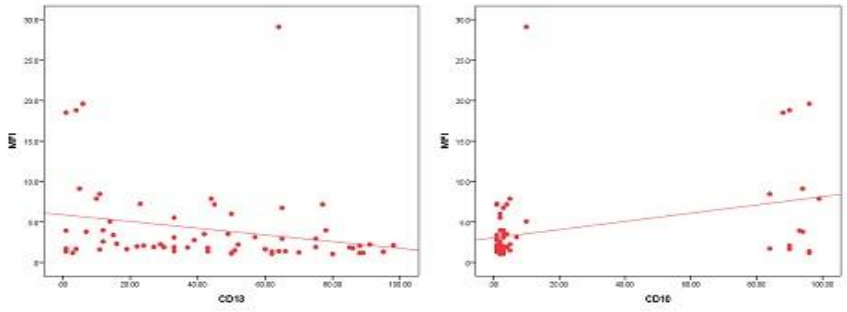


**Fig (3):** CD71 MFI negatively correlates with CD13 and positively correlates with CD10.

When comparing both CD71 expression and MFI between various leukemia subtypes, we found that the highest CD71 expression was for M7>M0>M3>M1>M2>M4>M5>>>>Precursor B-ALL while MFI was the highest in M7> Precursor B-ALL> M2,M3>M0>M1>M4>M5 (table 6 and figures 4&5).

**Table (6):** Comparison between different leukemia subtypes regarding both CD71 expression and MFI:

| Type | CD71 | MFI |
|---|---|---|
| | Median (IQR) | Median (IQR) |
| Precursor B | 3.87 (2.13 – 13.96) | 4.5 (1.9 – 13.8) |
| M0 | 82.9 (82.9 – 82.9) | 2.3 (2.3 – 2.3) |
| M1 | 78.5 (48.3 – 83.2) | 2 (1.9 – 2.6) |
| M2 | 53.05 (44.2 – 69.2) | 2.6 (1.4 – 3.5) |
| M3 | 81.15 (49.55 – 86.25) | 2.6 (2.1 – 5) |
| M4 | 41.6 (22.5 – 46.5) | 1.8 (1.2 – 2.9) |
| M5 | 19.5 (13.6 – 25.7) | 1.3 (1.3 – 1.8) |
| M7 | 88 (83.8 – 90) | 15 (12.5 – 17.2) |
| $X^2$ | 10.448 | 7.623 |
| P-value | 0.000 | 0.000 |

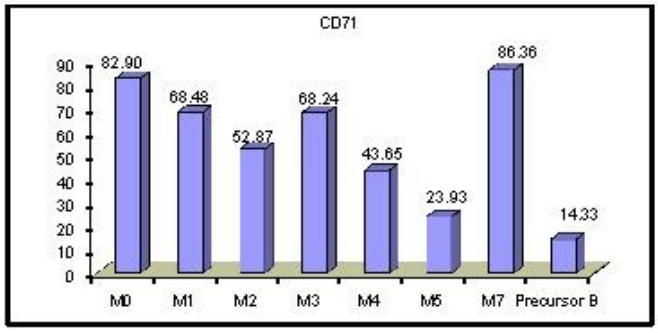


**Fig 4:** Pattern of CD71 expression among studied leukemia subtypes.

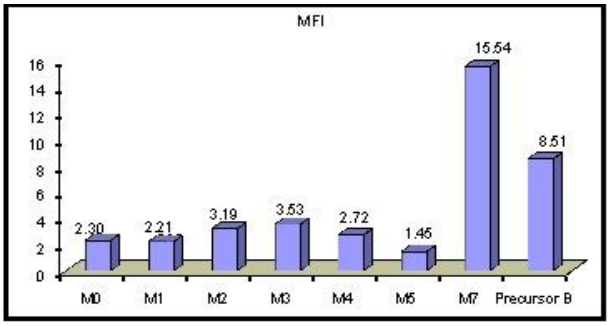


**Fig.5:** Pattern of CD71 MFI among studied leukemia subtypes.

## Discussion

There is a relation between antigens expressed by the tumor and its proliferation; and so, it is sensible to explore the correlation of the pattern of antigen expression with tumor behavior and treatment prognosis. CD71, the tranferrin receptor, is mandatory for iron transport into cells which is necessary for growth and proliferation,

hence, its wide distribution on both normal tissues with high dividing potential i.e. hematopoietic cells and malignant tissues, with the latter showing even higher expression.

In many studies [6,18,20-23,26-32], CD71 was found not only to be expressed by the majority of acute leukemias, chronic granulocytic leukemias in blast crisis, myeloma and lymphoproliferative disorders with variable density expression but also correlates with clinical data, morphologic subtypes, disease course and overall prognosis.

Our study aimed at evaluation of CD71 expression in acute leukemia.

We found that CD71 expression was significantly higher in acute myeloid leukemias than precursor B lymphoblastic leukemia while mean fluorescence intensity (MFI) of CD71 was significantly higher in precursor B lymphoblastic leukemia than acute myeloid leukemia. Similar to Liu et al[28] who studied CD71 expression in Chinese population and found that CD71 may be useful for the differential diagnosis of B-ALL from AML. Also Pande et al. [33] found that the Majority of AMLs showed positivity for CD71, being positive in 84% of the cases while The CD71 positivity rate was only 30% in cases of B-ALL.

Liu et al [28] found that acute megakaryocytic leukemia cases expressed CD71 on leukemic cells the highest, with the mean±SD of expression percentage was 80.16±8.23% (IQR: 74.27%-92.33%, median 77.03%) and that of MFI was 14.61±6.31 (IQR: 9.09-23.65, median 12.84) similar to our median and IQR 88 (83.8 – 90) and MFI 15 (12.5– 17.2).

Also, in our study, the mean±SD of CD71 expression percentage and MFI of poorly differentiated myeloid leukemias (M0, M1, M2, M4) were 55.17±23.97 and 2.77±1.91 respectively. These results are near to those by Liu et al [28] which were 39.14±26.37% for expression percentage and 9.9±11.9 for MFI.

Regarding partially differentiated AML: Acute promyelocytic leukemia (APL) in our study had high CD 71% expression and MFI 81.15 (49.55 – 86.25) 2.6 (2.1 – 5) respectively in contrast to Liu et al [28] and AMoL in our study had low CD 71% expression and MFI 19.5 (13.6 – 25.7), 1.3 (1.3 – 1.8) respectively similar to Liu et al.[28].

Acute lymphoblastic leukemias in our study were all of precursor B type with low % expression 3.87 (2.13 – 13.96) and MFI 4.5 (1.9 – 13.8), similar to Liu et al [28] who found B- ALL had % expression 9.63±9.77% (0.47%-39.23%, median 7.49%), with the MFIR of 1.93±1.1 (1.13-6.8, median 6.8).

These results were in contrast to El-Menshawy et al. [34] who studied CD71 expression in Egyptian population and demonstrated that CD71 is over expressed in ALL rather than AML.

When comparing different FAB subtypes of AML with each other regarding expression percentage and MFI, we found that the highest CD71 % expression was for M7 then poorly differentiated AML (M0, M1, M2, M4) then partially differentiated AML while precursor B-ALL was negative for this marker despite being of higher fluorescence intensity than AML similar to results by Liu et al [28] except for AML M3 which despite being partially differentiated however showed higher expression than most of poorly differentiated AML.

However, in contrast to El-Menshawy et al.[34] who found that there was an increased expression of CD71 in AML, M3, M4, and M5, partially differentiated myeloid leukemia with little maturation evidence along with high proliferation capacity.

The difference between our results and that of Menshawy et al. [34] may be due to reliance of the latter on MFI as a measure of antigenic expression.

Both Park et al. [35] and Liu et al. [28] also demonstrate that acute erythroblastic leukemia (AEL) patients do not necessarily express CD71 on their leukemic cells (included myeloblasts and erythroblasts) i.e. CD71 is not a specific and/or reliable marker for AEL. Koehler et al. [27] and Płoszyńska et al. [36] studied CD71 expression on ALLs and found more frequent expression of CD71 on T-ALLs than on B-ALLs. We were unable to observe CD71 expression on AEL and

T-ALLs because no such cases were included in our study.

In our study, a significant positive correlation was found between CD71 expression and each of age, common myeloid markers; CD13, CD33,CD117 and a significant negative correlation with CD14 and HLA-DR and common lymphoid markers; CD10, CD19, CD20, CD5. A significant negative correlation was found between mean fluorescence intensity of CD71 and each of age, TLC, CD13 and CD14 and a significant positive correlation with common lymphoid markers; CD10, CD19, CD20 while showed no significant correlation with any of clinicopathologic features.

These results were in comparison to El-Menshawy et al. [34] who found CD71 expression to correlate positively with total leukocyte count in ALL patients and negatively with platelet count in AML cases and Das Gupta et al. [22] in his study at an Indian population where no significant correlation with Hb or platelet count could be found but a significant negative correlation with platelet count in AML was found, and Kollia et al. [37] who concluded in his molecular analysis of CD71 mRNA expression in AML that no statistically significant correlation were found with specific FAB classification.

In conclusion, we suggest CD71 to be useful in differentiation of acute myeloid leukemia from precursor B ALL and further help in discriminating the differentiation status of AML.

However, further prospective studies are needed to document possible relation of CD71 with response to treatment and relapse rate. Also, studies relate CD71 with clonal evolution in leukemia may predict possibility to be an imporant molecular target in future therapy of acute leukemia.

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