ORIGINAL ARTICLE

PROGNOSTIC IMPACT OF CD34 EXPRESSION IN PAEDIATRIC PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKAEMIA

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Background: Acute lymphoblastic leukaemia (ALL) affects adults as well as children. Malignant transformation and proliferation occur in lymphoid progenitor cells found in bone marrow, blood, and extra-medullary locations. Precursor B-cell types account for the majority of ALL cases. Objective was to measure the expression of CD34 positive cells as a prognosis-related marker in paediatric Acute Lymphoblastic Leukaemia (ALL). It was a prospective cohort study, conducted at the Armed Forces Institute of Pathology, Rawalpindi, from July 2022 till July 2023. **Methods:** This study investigates the expression of CD34, a marker associated with hematopoietic stem and progenitor cells, in paediatric ALL and its correlation with clinical outcomes. Our study included 122 children aged 18 years or younger, newly diagnosed with ALL. Patients were diagnosed on complete blood counts and initial bone marrow examination, followed by flow cytometry. Essential molecular and cytogenetic studies were also carried out, followed by "day 29" induction marrow to assess the remission status of the patients under treatment protocols. CD34 expression was measured by flow cytometry and correlated with the clinicohaematological parameters of the patients for identification of risk groups. **Results:** The study comprised of 78 (63.9%) males and 44 (36.1%) females. Overall, 79% of patients showed CD34 expression while its expression was absent in 21% patients. CD34 expression was correlated with higher total leucocyte count, increased peripheral blood blast percentage, decreased platelet count and increased transfusion dependency. Minimal residual disease status was significantly better in CD34 negative patients as compared to CD34 positive patients. **Conclusion:** Expression of CD34 is an adverse prognostic marker in ALL patients and the presence of this antigen affects the clinical outcome of these patients.

Keywords Acute lymphoblastic leukaemia (ALL); CD34 expression; Paediatric; Remission status

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INTRODUCTION

Acute lymphoblastic leukaemia (ALL) affects adults as well as children. Malignant transformation and proliferation occur in lymphoid progenitor cells found in bone marrow, blood, and extra-medullary locations.[1] Precursor B-cell types account for the majority of ALL cases.[2] Early symptoms of the illness include lymph node enlargement, lethargy, appetite loss, bone pains, and abdominal distention due to splenomegaly and hepatomegaly. Whereas chronic leukaemia progresses over months, acute leukaemia advances quickly over weeks.[3] The development of ALL is largely influenced by three factors: radiation exposure, prior cancer treatment, and genetic abnormalities.[4]

Targeted medicines and improved risk stratification are necessary since some patients still experience relapse or resistance to treatment. Many treatments related toxicities are decreased by altering the treatment plans and in the treatment of paediatric haematological patients, the development of safer medicines has taken priority. About 26% of childhood malignancies are caused by ALL.[5] Children with ALL now have a much better prognosis than they had a few decades ago and in the developed countries, 5-year survival rates are currently over 90%.[5]

Utilizing multiple immunophenotype markers is necessary, since there is an overlap in the expression of some markers in acute leukaemia. Flow cytometry panel results have varied in the research conducted on ALL immunophenotyping.[6] Transmembrane glycoprotein CD34 is expressed on progenitor cells, endothelial cells, and early lympho-hematopoietic stem cells and it is an important immaturity marker.[7] In children with acute leukaemia, a high percentage of CD34 cells positivity has been linked with clinical characteristics, suggesting that it could be a predictive marker for prognosis and risk stratification.[8]

The expression of CD34 in ALL patients determines their clinical relevance and prognosis. It is possible for

leukemic cells to infiltrate an organ in patients with ALL and significant side effect of the disease relapse is infiltration, which is associated with a poor prognosis. An ongoing barrier to long-term remission in ALL is infiltration of the central nervous system (CNS) and the testes.[9]

CD34 positivity has been related with poor markers such as a higher percentage of peripheral blood blasts, a lower platelet count, and a higher total leucocyte count. The persistence of blasts in the bone marrow aspirate following one session of induction chemotherapy was linked to CD34 positivity.[10] In addition to a decrease in the expression of cell cycle genes, high CD34 expression was linked to a poor response to therapy, as well as an excess of genes involved in cell motility and adhesion, axonal guidance, and the inhibition of apoptosis. It shows a higher leukaemia-initiating potential.[11]

MATERIAL AND METHODS

This prospective cohort study was carried out at, Department of Haematology & Immunology, AFIP, Rawalpindi, from June –Dec 2023 after approval from Ethical Review Board under IRB-No: IRB/24/2699 using non-probability consecutive sampling technique. All the procedures in the study were done in accordance with the ethical standards of our local institutional committee and with the 1964 Helsinki declaration. Detailed clinical data were noted on a Proforma after informed verbal and written consent was obtained from all the parents of the children included in the study.

Sample size of our study was calculated by using the WHO sample size calculator. Based on 2.5 times higher relative risk of remission failure due to CD34 positivity, the minimum sample size calculated was 61 with the confidence level of 99. Relative Precision of 0.50 and anticipated probability of disease among exposed and unexposed being 55% and 22% respectively.

Our study included 122 paediatric patients under the age of 18 years, both genders and newly diagnosed with ALL. Previously diagnosed ALL patients presenting with relapse, those who required induction treatment other than the usual. Protocol and those having other acute leukaemias and who were lost to follow up were excluded from the study.

Patients were provisionally diagnosed on complete blood counts (CBC) and initial bone marrow examination morphology, followed by Immunophenotypes by Flow cytometry. Essential molecular and cytogenetic studies were also carried out, followed by "day 29" induction marrow to assess the remission status of the patients. CD34 expression was measured and correlated with the clinicohaematological parameters of the patients for identification of risk groups.

Automated haematology analyzer (Sysmex XN3000) was used to perform complete blood counts. Bone marrow aspirate and biopsy samples were collected. Peripheral blood and aspirate films were stained with Leishman, Giemsa and Sudan Black B stains for morphology and cytochemistry. Trephine biopsies sections were stained with haematoxylin and eosin and immunohistochemistry were also applied. All patients of ALL were diagnosed according to WHO's classification with the integration of clinical data, morphology, cyto-chemistry and flowcytometry.[12]

Immunophenotyping was performed on every patient for definitive diagnosis. Three colour flow cytometry was performed on the BD FACSCanto 3 COLOR Flow Cytometer using monoclonal antibodies. Whole blood/ marrow aspirate samples were used followed by addition of fluorescently conjugated antibodies according to standard protocol.

Molecular analysis for ALL genetic mutations was done as per routine procedure. LSM (Lymphocyte separation medium) method was used to extract RNA first from the sample and transformed to complementary DNA using reverse transcriptase PCR(RT-PCR). DNA was assessed on NanoDrop (Thermo Fisher Scientific) for quality and quantity. Complementary DNA was amplified in a multiplex Polymerase Chain Reaction (Real-time PCR). by using specific primers.

Cytogenetic examination was done by using conventional Giemsa banding method by Metaphase chromosome banding. Samples collected in sodium heparin tube were handled immediately for analysis and karyotypes defined as per International System for Human Cytogenetic Nomenclature.[13] Cytogenetic analysis was grouped as hyperdiploidy (chromosomes 51–66), hypodiploidy, (<46chromosomes), t (9;22) and miscellaneous chromosomal abnormalities.

On day 29 of the treatment, induction bone marrow was done to assess the remission status of the patient's remission was defined as <5% blasts cells on morphology in the presence of an overall haematological recovery (Neutrophils $>1.0x10^9$/L, platelets $>100x10^9$/L), and no transfusion dependency and absence of extramedullary disease upon end of induction therapy.[14]

CD34 expression was measured and correlated with the clinicohaematological parameters of the patients for identification of risk groups. The patients were classified into two groups. Low risk group included those with age ≤11 years, TLC ≤50x 10^9/L, Cytogenetic hyperdiploidy, and absence of CNS disease. Those with age (≤1 year), male gender, TLC ≥50x 10^9/L, Cytogenetic abnormality t (9;22),

BCR-ABL-1 and CNS involvement were stratified into a high-risk group.[15]

UK ALL 2011 treatment protocol for induction chemotherapy was given for low-risk patients as Regimen A (Vincristine, Dexamethasone and Asparaginase) and in high-risk Regimen B (Dexamethasone, Vincristine, Daunorubicin and Asparaginase) were given.

The data was analyzed on Statistical package of social sciences version 26. Mean & standard deviation, frequency and percentages were calculated. The Relative Risk, paired t test, and spearman correlation coefficient were applied (for quantitative variables) and chi square test (for qualitative variables). P-value of less than 0.05 was considered significant.

RESULTS

A total of 122 paediatric participants were included in this study, with 78 (63.9%) being males and 44 (36.1%) females. The median age of patients was 9 years with IQR of 11.50–5.00. The distribution of clinical and demographic characteristics among paediatric patients with Acute Lymphoblastic Leukaemia are shown in Table-1.

The comparison of the platelets count, total leukocyte count and blast cell count between paediatric Acute Lymphoblastic Leukaemia (ALL) patients with CD34 positive expression (CD34+) and those with CD34 negative expression (CD34-) is shown in Table-II. The median platelets count has significantly lower in CD34+ patients (78.0, IQR 98.5–63.0) compared to CD34- patients (211.0, IQR 277.0–176.0), with a p-value of <0.001. Additionally, CD34+ patients had a significantly higher median total leukocyte count (15.7, IQR 18.2–8.1) than CD34- patients (8.7, IQR 10.7–7.7), with a p-value of 0.007. Moreover, CD34+ patients had a significantly higher median total blast cell count (9.0, IQR 16.0-3.0) than CD34- patients (3.0, IQR 7.0-2.0), with a p-value of 0.001. These findings indicate that CD34 expression is associated with lower platelet counts, higher leukocyte counts and higher blast cell count.

The association of various clinical and laboratory features with CD34 expression in pediatric ALL patients is shown in Table-3. The data shows that CD34 positive patients are more likely to have splenomegaly (62.5% vs. 37.5%, p=0.020), hepatomegaly (83.3% vs. 16.7%, p<0.001), and lymphadenopathy (74.6% vs. 25.4%, p<0.001) compared to CD34 negative patients. Additionally, CD34 positive patients are significantly more likely to have a low platelet count (83.9% vs. 16.1%, p<0.001), high total leukocyte count (74.1% vs. 25.9%, p<0.001), and transfusion dependency (81.8% vs. 18.2%, p<0.001). CD34 positive patients also showed a higher incidence of abnormal cytogenetics (72.2% vs. 27.8%, p=0.001), high-risk stratification (61.5% vs. 38.5%, p<0.001), and positive minimal residual disease (MRD) status (65.2% vs. 34.8%, p<0.001). These findings suggest that CD34 expression is associated with more severe clinical features and poor prognostic factors in paediatric ALL patients.

CD34-positive patients showed significantly higher rates of splenomegaly (RR = 2.31), hepatomegaly (RR = 16.25), lymphadenopathy (RR = 11.76), low platelet count (RR = 19.40), high TLC (RR = 6.40), transfusion dependency (RR = 31.50), and abnormal cytogenetics (RR = 0.264). Additionally, CD34-positive patients were more likely to have BCR-ABL positivity (RR = 2.73) and blast cells >5% (RR = 0.220). CNS involvement and higher risk stratification are also more prevalent in CD34-positive patients. Remission is less common in CD34-positive patients (RR = 0.318), indicating poorer outcomes.

Table-1: Distribution of clinical and demographic characteristics in paediatric patients with acute lymphoblastic leukaemia (n = 122)

Variables		n (%)
Gender	Male	78 (63.9)
	Female	44 (36.1)
CD34 Expression	Positive	61 (50.0)
	Negative	61 (50.0)
Splenomegaly	Yes	48 (39.3)
	No	74 (60.7)
Hepatomegaly	Yes	54 (44.3)
	No	68 (55.7)
Lymphadenopathy	Yes	67 (54.9)
	No	55 (45.1)
Platelets Count	Low	56 (45.9)
	Normal	66 (54.1)
TLC	High	54 (44.3)
	Normal	68 (55.7)
Transfusion Dependency	Yes	66 (54.1)
	No	56 (45.9)
Cytogenetic	Normal	86 (70.5)
	Abnormal	36 (29.5)
BCR ABL 1	Positive	20 (16.4)
	Negative	102 (83.)
Blast cells	<5%	64 (52.5)
	>5%	58 (47.5)
Risk Stratification	High	91 (74.5)
	Low	31 (25.4)
Remission Status	In Remission	63 (51.6)
	Not in Remission	59 (48.4)

Table-2: Comparison of Platelets Count, Total Leukocyte Count and Blast Cell Count between CD34 Positive and CD34 Negative Paediatric ALL Patients

	CD34		*p*-Value
	Positive Median, IQR	Negative Median, IQR	
Platelets Count	78.0 (98.5-63.0)	211.0 (277.0-176.0)	<0.001
Total Leukocyte Count	15.7 (18.2-8.1)	8.7 (10.7-7.7)	0.007
Blast Cell Count	9.0 (16.0-3.0)	3.0 (7.0-2.0)	0.001

Table-3: Association of Clinical and Laboratory Features with CD34 Expression in Paediatric ALL Patients

Variables		CD34		Total	*p*-value	RR
		Positive	Negative			
Splenomegaly	Yes	30 (62.5%)	18 (37.5%)	48 (39.3%)	0.020	2.31
	No	31 (41.9%)	43 (58.1%)	74 (60.7%)		
Total		61 (50.0%)	61 (50.0%)	122 (100%)		
Hepatomegaly	Yes	45 (83.3%)	9 (16.7%)	54 (44.3%)	<0.001	16.25
	No	16 (23.5%)	52 (76.5%)	68 (55.7%)		
Total		61 (50.0%)	61 (50.0%)	122 (100%)		
Lymphadenopathy	Yes	50 (74.6%)	17 (25.4%)	67 (54.9%)	<0.001	11.76
	No	11 (20.0%)	44 (80.0%)	55 (45.1%)		
Total		61 (50.0%)	61 (50.0%)	122 (100%)		
Platelets Count	Low	47 (83.9%)	9 (16.1%)	56 (45.9%)	<0.001	19.40
	Normal	14 (21.2%)	52 (78.8%)	66 (54.1%)		
Total		61 (50.0%)	61 (50.0%)	122 (100%)		
TLC	High	40 (74.1%)	14 (25.9%)	54 (44.3%)	<0.001	6.40
	Normal	21 (30.9%)	47 (69.1%)	68 (55.7%)		
Total		61 (50.0%)	61 (50.0%)	122 (100%)		
Transfusion Dependency	Yes	54 (81.8%)	12 (18.2%)	66 (54.1%)	<0.001	31.50
	No	7 (12.5%)	49 (87.5%)	56 (45.9%)		
Total		61 (50.0%)	61 (50.0%)	122 (100%)		
Cytogenetic Abnormality	Normal	35 (40.7%)	51 (59.3%)	86 (70.5%)	0.001	0.264
	Abnormal	26 (72.2%)	10 (27.8%)	36 (29.5%)		
Total		61 (50.0%)	61 (50.0%)	122 (100%)		
BCR ABL-1 mutation	Positive	14 (70.0%)	6 (30.0%)	20 (16.4%)	0.043	2.73
	Negative	47 (46.1%)	55 (53.9%)	102 (83.6%)		
Total		61 (50.0%)	61 (50.0%)	122 (100%)		
Blast cells	<5%	21 (32.8%)	43(67.2%)	64 (52.5%)	<0.001	0.220
	>5%	40 (69.0%)	18 (31.0%)	58 (47.5%)		
Total		61 (50.0%)	61 (50.0%)	122 (100%)		
CNS Status	CNS Involvement	6 (85.7%)	1 (14.3%)	7 (5.7%)	0.057	6.55
	No CNS Involvement	55 (47.8%)	60 (52.2%)	115 (94.3%)		
Total		61 (50.0%)	61 (50.0%)	122 (100%)		
Risk Stratification	High	56 (61.5%)	35 (38.5%)	91 (74.6%)	<0.001	8.32
	Low	5 (16.1%)	26 (83.9%)	31 (25.4%)		
Total		61 (50.0%)	61 (50.0%)	122 (100%)		
Remission Status	In Remission	21 (33.3%)	42 (66.7%)	63 (51.6%)	0.002	0.238
	Not in Remission	40 (67.8%)	19(32.2%)	59 (48.4%)		
Total		61 (50.0%)	61 (50.0%)	122 (100%)		

DISCUSSION

Acute lymphoblastic leukaemia represents 30% of all malignant tumours and 80% of childhood leukaemia. It is the most prevalent malignant tumour in children, with an incidence of 3–5 per 100,000.[16] In Pakistan, the lack of a tumour registry prevents access to statistical data on the prevalence and incidence of malignancies such as leukaemia. However, there are some studies and data that provide insights into the situation.[17,18] The normal production of red blood cells (RBCs), white blood cells (WBCs), and platelets by the bone marrow is disrupted by this medical condition, which increases the risk of anaemia, recurrent infections, and bleeding tendency. Additionally, blast cells have the ability to migrate from the bone marrow to other organs, including the liver, spleen, lymph nodes, and central nervous system, where they may congregate and cause additional problems.[19]

One hundred twenty-two patients were included in this study, which provided significant new insights into the clinical characteristics and demographic factors associated with paediatric ALL. The results draw attention to certain crucial points. Males made up a larger share of the study population than females. These results were similar with study

conducted by Ahmed *et al*., 2023 in which (63.2%) ALL patients were males.[20]

The study findings shed important light on the clinical and demographic traits of young patients with ALL, with a special emphasis on the relevance of CD34 expression. This study reported and found that CD34 expression was found to be positive in many patients less than 5 years (50%) of patients and among B-cell ALL (88%). Our study found that CD34 positive expression is linked to a more severe disease phenotype that includes higher leukocyte and platelet counts, as well as a higher frequency of unfavourable prognostic markers such positive minimal residual disease (MRD) status and aberrant cytogenetics. The study conducted by Shah *et al*., in 2018 showed similar results and CD34 expression was linked to unfavourable indicators such as a higher percentage of peripheral blood blasts, a lower platelet count, and a higher total leucocyte count. Its expression is linked to indicators of poor prognosis.[21]

A significant correlation was seen between CD34 positivity and clinical features, such as splenomegaly (p=0.001), hepatomegaly (p=0.001) and lymphadenopathy (p=0.001). Moreover, patients who were CD34-positive exhibited significantly higher total leucocyte count (TLC) compared to those who were CD34-negative (p=0.007). Conversely, there were no significant differences in haematocrit and haemoglobin between the two groups.

The strong correlation between CD34 positivity and younger age, particularly in patients below 5 years, aligns with present literature. This research indicates that CD34 expression is more common in paediatric patients with B-ALL compared to older children and adults.[22]

Furthermore, our findings regarding the correlation between CD34 expression and B-ALL are consistent with previous studies. These studies have demonstrated that CD34-positive B-ALL is linked to improved treatment response and overall prognosis.[23] Nevertheless, the lack of substantial differences in other haematological parameters, including haemoglobin and haematocrit, is inconsistent with previous research that reported more marked differences.[24]

The high total leukocyte count observed in CD34-positive patients suggests that these patients may experience an aggressive disease course. This is in similar to the typical association between elevated total leukocyte count and a worse prognosis in leukaemia.

The association of CD34 with younger age groups may be explained by the increased proliferative capacity of hematopoietic stem cells during early childhood. CD34 serves as a marker of stem cell immaturity, and its expression may be more prevalent in younger individuals due to their higher proportion of immature stem cells.[25]

The strong correlation with CNS involvement and mediastinal masses suggests that CD34 expression may contribute to leukaemia dissemination, though further research is needed to elucidate this mechanism.[26]

The prognosis of paediatric ALL is substantially predicted by MRD (minimum residual disease) values. MRD levels do not correlate with the total leukemic cell count at diagnosis; however, the CD34+/CD38− subpopulation seems to be especially associated with this connection. A higher CD34+/CD38− percentage may indicate a greater number of leukemic stem and progenitor cells, as studies show that leukemic stem cells are enriched in the CD34+/CD38− subgroup, which is seen in both Acute Myeloid Leukaemia and Acute Lymphoblastic Leukaemia. These results are similar to our findings.[27]

Patients with the CD34+ phenotype experienced a rise in incomplete remission and relapse. According to the study of Attia *et al*., in 2020, a large percentage of patients with a CD34+ phenotype had a poor prognosis for paediatric ALL and a higher risk of relapse, both of which were statistically correlated with their result.[28]

There is a correlation between CD34 positivity and increased rates of high-risk stratification and aberrant cytogenetics. The existence of the Philadelphia chromosome or other chromosomal abnormalities are examples of abnormal cytogenetic profiles, which are well-established prognostic markers in ALL. Our results are consistent with those of Schrappe *et al*., 2012, showing that after 4 weeks of induction chemotherapy, a small but considerable number of patients fail to attain complete remission. Most patients with first induction failure experience an early relapse, while some never experience complete remission. An even poorer prognosis was given by the more common traditional adverse prognostic markers, which included a high leukocyte count, advanced age, and t (9;22) (BCR-ABL1) positive.[29]

The percentage of CD34+ cells in paediatric ALL was reported to be associated with extramedullary infiltration, poor response to chemotherapy, elevated peripheral blood blast count, and high WBC count, low platelet counts and transfusion dependency. Our results show similarity with the results of Al-Kubayasi ASI *et al*., 2024stating that there was a trend toward a greater proportion of proliferating cells in CD34+ leukemic subpopulations. Heterogeneity detection and subpopulation property analysis are useful applications in the diagnosis of relapsed leukaemia, monitoring, and forecasting of challenges in minimal residual illness detection in acute leukaemia using flow cytometry.[30]

The results of this study indicate that CD34 marker expression may be a valuable prognostic indicator in paediatric leukaemia. Specifically, CD34 expression may help identify patients who are at a higher risk groups of developing CNS involvement, extramedullary haematopoiesis, transfusion dependency and bone marrow infiltration by blast cells.[31]

This information could guide clinicians in making more informed decisions regarding the intensity of treatment, such as implementing more aggressive therapies or initiating CNS-directed treatment.[32]

The association between CD34 positivity and B-ALL strengthens the notion that CD34 could serve as a promising target for future immunotherapeutic approaches aimed at treating B-ALL.[33]

This study's strengths include a robust sample size (122), well-defined patient risk stratification groups, and the use of well-known markers like CD34. Its focus on the relationship between CD34 expression and detailed clinical outcomes, such as CNS involvement, organomegaly, bone marrow infiltration by blasts adds substantial value to the current literature.

Limitations

Lack of large-scale, multi-centre trials and methods for assessing expression levels restrict the investigation of CD34 expression in paediatric ALL.

CONCLUSION

It is concluded that CD34 positive cells have the ability to spread leukaemia and are linked to a poor prognosis and survival rate. Additionally, a high proportion of CD34 cells is positively correlated with biological and clinical features such as advanced risk classification, age, high peripheral WBC count, high PB blast cell count, poor karyotype, unfavourable fusion gene, high incidence of extramedullary infiltration, and a dismal chemotherapy response. As a result, for paediatric ALL, the CD34 fraction may be a valuable prognostic measure and guide for customized therapy. Additional research is required to validate our results and clarify the precise reason.

AUTHORS' CONTRIBUTION

All the authors contributed equally in the manuscript, i.e., conceptualization of the study design, literature search, proof reading, write-up.

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