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Dynamics of haematological parameters in the prediction of relapse in B-Acute lymphoblastic leukemia.

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Abstract:

Background: Relapse of disease is the ultimate cause of poor survival in B-Acute lymphoblastic leukemia (B-ALL) and the biggest challenge to treat. With the availability of novel therapies, including targeted therapies, the survival of relapsed patients can be improved if it can be detected at its initial stage. Although many studies have identified risk factors associated with a high probability of relapse, there is no clear indicator that can indicate impending relapse in its initial stage.

Objectives: To investigate the utility of Complete blood cell count (CBC) parameters in predicting impending relapse in pediatric B-ALL patients.

Method: In this retrospective study, we studied 90 pediatric B-ALL patients with age ≤16years, including 30 relapse cases and 60 cases without relapse, registered from January 2015 to June 2015. All these B-ALL cases were diagnosed and treated in Tata Memorial Centre (TMC), Mumbai.

Laboratory parameters were noted from the TMC's electronic medical records (EMR).

17 Complete blood count (CBC) parameters included were studied at three time points in patients with relapse i.e. 3-6 months before relapse, 1-3 months before relapse and at the time of relapse. While in non-relapse patients, time point studied was at 2 years follow-up from initiation of therapy or last follow-up documented in the EMR.

Result: Of the 17 CBC parameters studied, platelet count (p=0.026) at 1-3 months before relapse was significantly associated with B-ALL relapse.

Similarly, there was a significant difference between the CBC parameters at the time of relapse with reduced hemoglobin (p=0.015), RBC count (p=0.001), platelet count (p<0.001), absolute neutrophil count (p<0.01), % neutrophil (p=0.037), % monocyte (p<0.01), % eosinophil (p<0.01), % large unstained cells (p<0.01).

No significant difference was seen between the relapse group (time point 3-6 months before relapse) and the non-relapse group (2 year follow-up / last follow-up).

The ROC - based cut off for Platelet count at the time-point of 1-3 months before relapse and 2yrs follow-up of non-relapsed patients was found to be 340 X 10^9/L (AUC of 62.9%) with 30% sensitivity and 97% specificity.

On the basis of Median platelet count of 244 X 10^9/L at time point of 1-3 months before relapse, the relative risk for platelet count was 1.462 (0.982, 2.174) with p-value 0.0612, which is close to significant value. Thus it showed that risk of getting relapse increases by 46.2% in patients with platelets <244 X 10^9/L as compared to platelets ≥244 X 10^9/L.

Conclusion: Thus, we concluded that platelet count have a high potential to predict impending relapse and provide a basis to investigate further for confirmation with ancillary tests. CBC testing is cheap and available in all laboratories. Hence it can be part of routine close monitoring of B-ALL patients.

(**Key words**: B-Acute lymphoblastic leukemia, Relapse, Complete blood count)

Introduction:

B-Acute lymphoblastic leukemia (B-ALL) is the most common aggressive type of blood cancer among children.[1] It is characterized by an over production of immature white blood cells called lymphoblasts or leukemic blasts in the bone marrow. These leukemic cells do not function like normal lymphocytes and are unable to effectively fight infection. The bone marrow is unable to make adequate numbers of red blood cells, normal white blood cells and platelets. Hence people with ALL become more susceptible to anaemia, recurrent infections, easy bruising and bleeding. Due to overcrowding of blast cells in the bone marrow, they can then spill out of the bone marrow into the blood stream and accumulate in various organs including the lymph nodes (glands), spleen, liver and central nervous system (brain and spinal cord) leading to organomegaly.

ALL can be of T or B ancestry. ALL arises in B-lymphocytes in the early stages of development in the bone marrow, hence the name precursor B-cell ALL or Pre B-cell ALL. Precursor B-cell acute lymphoblastic leukemia (B-ALL) is a hematological malignancy characterized by clonal proliferation of abnormal B-cell precursors (B-lymphoblasts) in the bone marrow [2].

Children under the age of 15 years constitute to approximately 85% of ALL and the remaining 15% of ALL cases are adults, mainly aged over 50 years. In children with ALL, 80% to 85% of ALL consists of early B-cells (also called precursor B-cell), 15% are early T-cells and approximately 2% are mature B-cells [3].

Previous group-level studies have identified many potential prognostic factors for childhood ALL, such as white blood cell (WBC) counts, age at diagnosis, response to prednisone and some gene fusions like BCR-ABL, TEL-AML1 and E2A-PBX1. Moreover, immunophenotype (T cell or B cell), percentage of lymphoblast in bone marrow (BM) on day 15 and day 33, level of minimal residual disease (MRD) also proven to be associated with a high probability of relapse risk for patients [4]. However, there is no clear indicator that can immediately indicate impending relapse in the coming few days or months. In current clinical practice ALL patients are closely monitored for clinical features such as fever of unknown origin, unexpected weight loss, new lymphadenopathy or organomegaly, etc. as well as Complete blood cell counts (CBC) monitoring at regular

interval.

Current risk- adapted treatments and supportive care have increased the survival rate to over 90% in developed countries. However the survival rate of B-ALL in Indian children is still less than 80% and approximately 20% of children who relapse have a poor prognosis, making B-ALL the leading cause of cancer mortality in pediatric disorders. The prediction of relapse in childhood B-ALL is a critical factor for successful treatment and follow-up planning.

The survival of relapsed patients can be improved if it can be detected at its initial stage. Although there are many genetics and baseline parameters for predicting of relapse but the major cause of death is frank relapse. There is no parameter which can predict impending relapse in its initial stage. Complete Blood Count (CBC) test, which is cheap and available in all laboratories, is regularly done to monitor blood counts in B-ALL patients. But the value of CBC is still not known. Hence we aim to conduct a systematic study of CBC parameters.

Objectives: To investigate the utility of Complete blood cell count (CBC) parameters in predicting impending relapse in pediatric B-ALL patients.

Materials and Methods: In this retrospective study, we studied 90 pediatric B-ALL patients with age ≤16years, including 30 relapse cases and 60 non-relapse cases from January 2015 to June 2015. Clinical evaluation and laboratory investigations were performed as a part of standard protocol.

The peripheral blood samples of B-ALL patients are processed for CBC testing at the time of TMC registration, on day 8 after the start of treatment and after every 15 days during 8 maintenance therapy. Blood samples for CBC test have been analyzed using state-of-art fully automated haematology analyzers like ADVIA 2120i, DxH 800 and XN 1000.

All patients were investigated for Complete blood count (CBC) after registration in Tata Memorial Centre (TMC). 17 CBC parameters included in the study were WBC count, RBC count, Platelet count, Hemoglobin cocentration, Mean Cell Volume (MCV), % Neutrophil, % Lymphocyte, % Monocyte, % Eosinophil, % Basophil, % Large unstained cells (LUC), Absolute Neutrophil count (ANC), Absolute Lymphocyte count, Absolute Monocyte count, Absolute Eosinophil count, Absolute Basophil count and Absolute LUC count.

Patient's demographic details, history of treatment and laboratory report data were obtained from the Electronic Medical Record (EMR) of TMC.

For relapse cases, three time-points investigated were 1-3 months before relapse, 3-6 months before relapse and relapse time point. For non-relapsed cases, time-point investigated was 2 years follow-up from initiation of therapy or last follow-up documented on EMR.

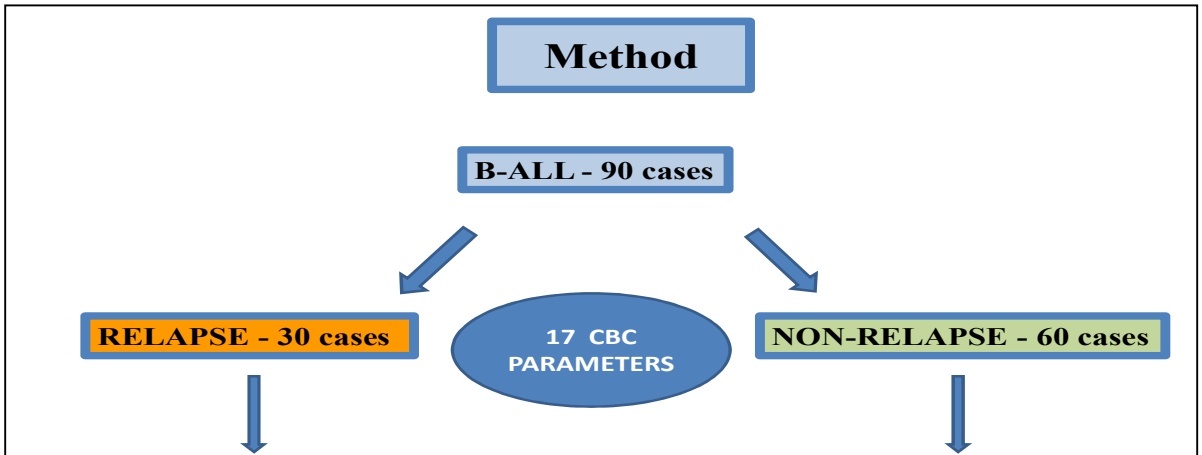

Figure 1. Distribution of B-ALL patients in relapse (n=30) and non-relapse (n=60) groups and comparison of various time points among the two groups.

Statistical analysis:

CBC parameters were compared between relapse and non-relapse patients. All continuous CBC parameters were reported using Median [IQR] and compared using the two-sample t-test for normal distribution and Wilcoxon rank-sum test for not normally distributed data. Categorical variables were reported as frequencies and percentages and **were** analysed by chi-square or Fisher's exact test as appropriate.

To determine the threshold for statistically significant CBC parameters in predicting impending relapse in pediatric B-ALL patients, the best cut-off **was** obtained through Youden's index. Odd's ratio and relative risk were evaluated for association between clinical and laboratory parameters and disease relapse. The distribution of significant CBC parameters in relapse and non-relapsed group **was** demonstrated using box plots. A p-value less than 0.05 was considered statistically significant for all tests.

All statistical analysis was performed using IBM SPSS version 29.

Results: 90 B-ALL patients were studied. 60 non-relapse patients included male 39 (65%) and female 21 (35%), while 30 relapse patients included male 19 (63%) and female 11 (37%). 17 CBC parameters of relapse and non-relapse groups were compared at different time points.

Table 1. Median age in relapse and non-relapse group

Age (in years)	Relapse	Non-relapse
Range	2 - 15	1-15
Median age	7.5	5.0

Table 2. Gender wise distribution in relapse and non-relapse group

Gender	Relapse	Non-relapse
Male	19	37

Female	11	23

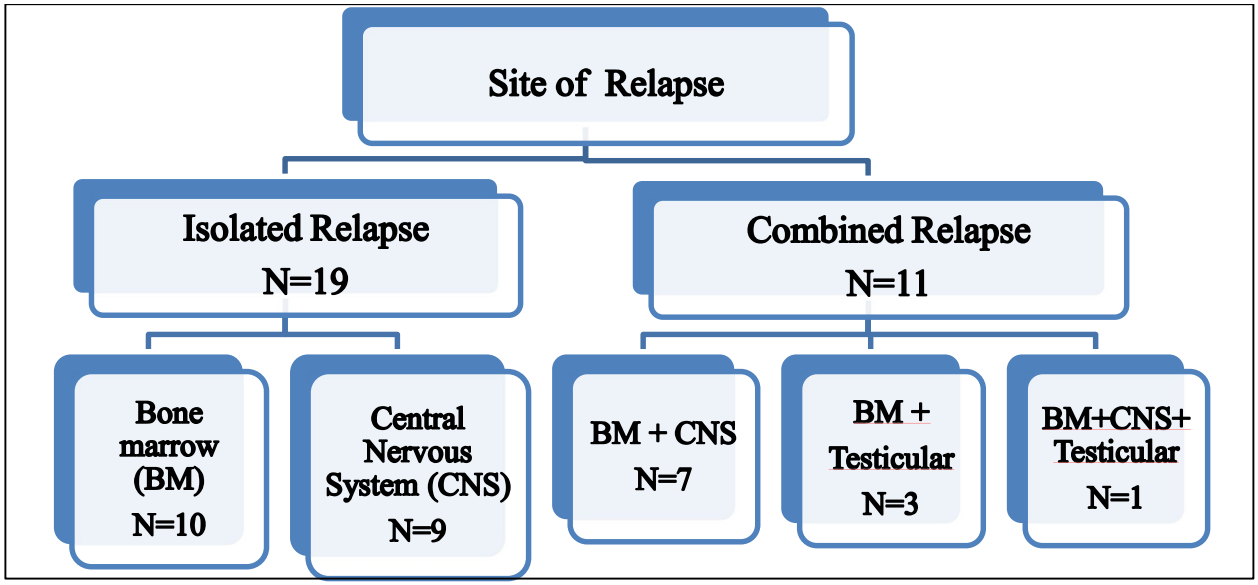

Figure 2. Distribution of relapse patients according to the site of relapse

In 30 relapse patients, the site of relapse was bone marrow (BM), central nervous system (CNS) and testis (in male patients). 19 patients had isolated relapse of BM (n=10) and CNS (n=9), while combined relapse was seen in 11 patients, which included BM & CNS (n=7), BM & testicular relapse (n=3) and BM, CNS & testicular relapse (n=1).

Table 3. Comparison between relapse group (1-3 months before relapse) and non-relapse group (2 years/last follow-up)

CBC Parameters	**Level**	**Relapse (n=30)**	**Non-Relapse (n=60)**	**p-value**
Timepoints		**1-3 months before relapse**	**2 yrs. / Last follow-up**	
HAEMOGLOBIN	median [iqr]	11.6 [10.8, 12.9]	12.6 [11.7, 13.4]	0.521
WBCCOUNT	median [iqr]	3.9 [3.1, 5.5]	6.7 [5.3, 8.3]	0.945
PLATELETS	median [iqr]	217 [170.0, 268.2]	270 [205.8,323.2]	0.048
MCV	median [iqr]	90.9 [84.8, 97.3]	85.1 [79.0, 90.3]	0.915
NEUTROPHIL%	median [iqr]	54 (13.4)	53 [46.4, 59.6]	0.286
LYMPHOCYTE %	median [iqr]	27.2 [21.4, 32.7]	34.2 [24.2, 38.9]	0.109

MONOCYTE %	median [iqr]	5.7 [4, 8]	5.0 [4.3, 6.2]	0.16
EOSINOPHIL %	median [iqr]	3.9 [2.8, 6.8]	3.2 [2.0, 6.9]	0.469
BASOPHIL %	median [iqr]	0.5 [0.3, 0.6]	0.6 [0.3, 0.8]	0.753
LUC %	median [iqr]	4.7 [3.4, 7.0]	3.0 [2.2, 3.8]	0.268
NEUTROPHIL ABS (ANC)	median [iqr]	2.3 [1.3, 3.1]	3.5 [2.5, 4.3]	0.706
LYMPHOCYTE ABS	median [iqr]	1.1 [0.7, 1.6]	2.0 [1.5, 2.7]	0.255
MONOCYTE ABS	median [iqr]	0.2 [0.2, 0.4]	0.4 [0.3, 0.4]	0.504
EOSINOPHIL ABS	median [iqr]	0.2 [0.1, 0.3]	0.2 [0.1, 0.4]	0.918
BASOPHIL ABS	median [iqr]	0 [0, 0]	0 [0.0, 0.1]	0.851
LUC ABS	median [iqr]	0.2 [0.1, 0.3]	0.2 [0.1, 0.3]	0.493

The comparison between relapse and non-relapse patients, for relapse patient's time point of 1-3 months before relapse was taken and for non-relapse patients 2 year follow-up or last follow-up from registration was considered. Of the 17 CBC parameters studied, platelet count (p=0.026) at 1-3 months before relapse was significantly associated with B-ALL relapse.

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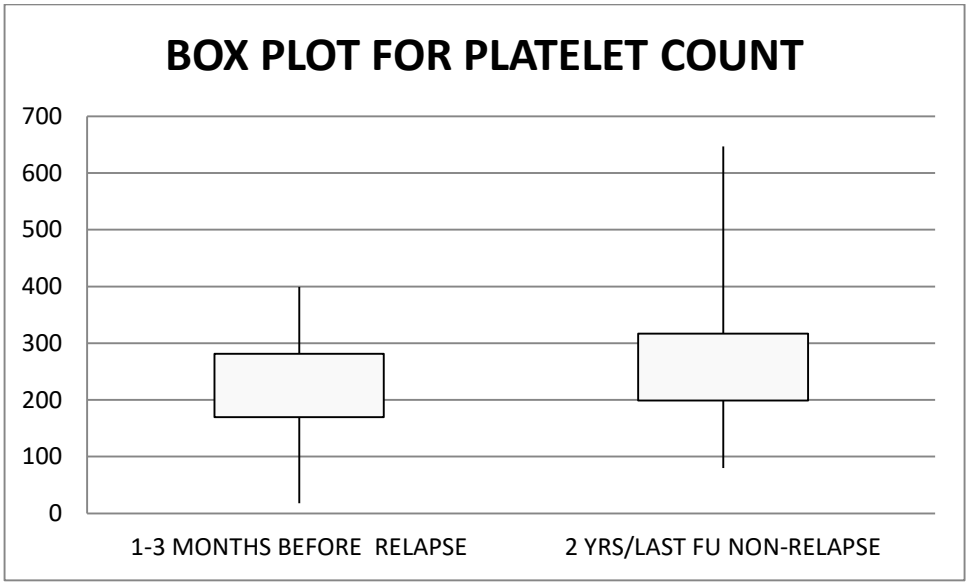
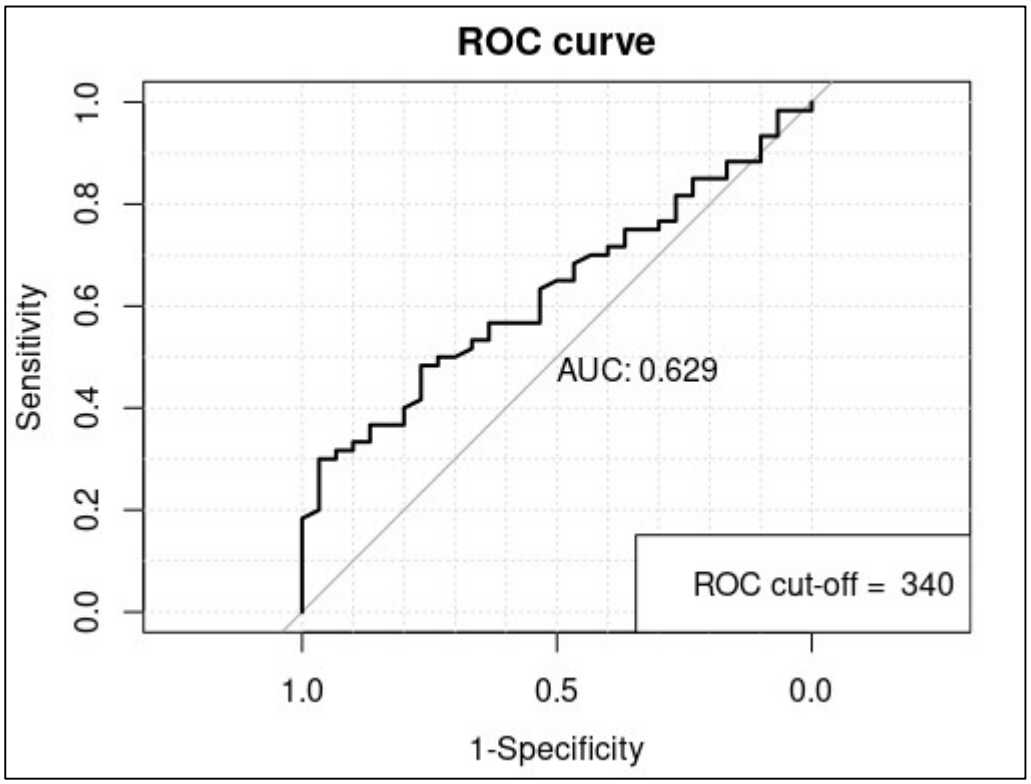


Figure 3. Box plot representing the count of Platelet parameter among relapse (for time point 1-3 months before relapse) and non-relapse group (2years follow up (FU) from initiation of therapy/ last follow-up). The distribution of CBC Platelet parameters with significant differences among the relapse and non-relapse cases is demonstrated using boxplots

ROC curve for platelete parameter for time point of 1-3 months before relapse and 2 years follow-up/last follow-up in non relapse:



Area Under the Curve estimates for classifying relapse			
Test Result Variable: PLATELET COUNT			
		95% Confidence Interval	
Area	P value	Lower Bound	Upper Bound
0.629	0.048	.514	.743

Figure 4. ROC curve for platelete parameter for time point of 1-3 months before relapse and 2 years follow-up/last follow-up in non relapse

From ROC curve, cut-off of platelet level is 340. The sensitivity is 30.0% & specificity is 97%.

Table 4. Cross tabulation of Median platelet count

Platelet median of 244 X 10^9/L * Relapse (1-3 months before relapse) & Non Relapse (2yrs/last follow up) - Cross tabu					
			Relapse	**Non relapse**	**Total**
Median platelet count	**< 244**	**Count**	**19**	**26**	**45**

of 244 X 10^9/L		**% within plt_cutoff_244**	**42.2%**	**57.8%**	**100.0%**
	≥ 244	**Count**	**11**	**34**	**45**
		% within plt_cutoff_244	**24.4%**	**75.6%**	**100.0%**

On the basis of Median platelet count of 244 X 10^9/L (from Table 3), cross tabulation between relapse group (time point of 1-3 months before relapse) and non-relapse group (time point of 2years follow-up from initiation of therapy) showed that the relative risk for platelet count was 1.462 (0.982, 2.174) with p-value 0.0612 (near to significance), which means that risk of getting relapse increases by 46.2% in patients with platelets <244 X 10^9/L as compared to platelets ≥244 X 10^9/L.

Time point 3-6 months before relapse: No significant difference was seen between the relapse group (3-6 months before relapse) and the non-relapse group (2 year follow-up / last follow-up).

Table 5. Comparison of CBC parameters between relapse (3-6 months before relapse) and non-relapse (2 years/last follow-up) group

CBC parameters	Level	Relapse (n=30)	Non-Relapse (n=60)	p-value
Time point		**3-6 months before relapse**	**2 yrs./ Last follow-up**	
HAEMOGLOBIN	median [iqr]	11.6 [10.9, 12.4]	12.6 [11.7, 13.4]	0.925
WBCCOUNT	median [iqr]	3.3 [2.4, 4.8]	6.7 [5.3, 8.3]	0.155
PLATELETS	median [iqr]	239.5 [199.2, 333.2]	270.0 [205.8,323.2]	0.518
MCV	median [iqr]	93.7 [84.8, 98.7]	85.1 [79.0, 90.3]	0.561
NEUTROPHIL %	median [iqr]	54.1 [44.3, 65.9]	53.0 [46.4, 59.6]	0.472
LYMPHOCYTE %	median [iqr]	25.9 [16.7, 34.1]	34.2 [24.2, 38.9]	0.257
MONOCYTE %	median [iqr]	6 [4.9, 8.5]	5.0 [4.3, 6.2]	0.623
EOSINOPHIL %	median [iqr]	5.3 [3.2, 8.0]	3.2 [2.0, 6.9]	0.962

BASOPHIL %	median [iqr]	0.3 [0.2, 0.5]	0.6 [0.3, 0.8]	0.079
LUC %	median [iqr]	4.1 [3.2, 6.7]	3.0 [2.2, 3.8]	0.641
NEUTROPHIL ABS (ANC)	median [iqr]	1.7 [1.2, 2.8]	3.5 [2.5, 4.3]	0.111
LYMPHOCYTE ABS	median [iqr]	1 [0.4, 1.5]	2.0 [1.5, 2.7]	0.966
MONOCYTE ABS	median [iqr]	0.2 [0.1, 0.4]	0.4 [0.3, 0.4]	0.336
EOSINOPHIL ABS	median [iqr]	0.2 [0.1, 0.3]	0.2 [0.1, 0.4]	0.614
BASOPHIL ABS	median [iqr]	0.011[0.005,0.011]	0.0 [0.0, 0.1]	0.046
LUC ABS	median [iqr]	0.1 [0.1, 0.3]	0.2 [0.1, 0.3]	0.382

In the comparison of CBC parameters between the relapse group (time point of 3-6 months before the relapse) and non-relapse group (time point of 2 years or last follow-up), no parameter was significant.

Table 6. Comparison of CBC parameters between relapse group (time point of relapse) & non-relapse group (2 years/last follow-up)

CBC Parameters	Level	Relapse (n=30)	Non-Relapse (n=60)	p-value
Time points	-	Relapse Time-point	2 yrs/Last follow-up	
HAEMOGLOBIN	median [iqr]	11.4 [9.0, 13.3]	12.6 [11.7, 13.4]	0.015
WBCCOUNT	median [iqr]	5.9 [3.3, 10.9]	6.7 [5.3, 8.3]	0.694
PLATELETS	median [iqr]	110.5 [40.5, 235.5]	270 [205.8,323.2]	<0.01
MCV	median [iqr]	88.6 [84.5, 95.4]	85.1 [79.0, 90.3]	0.046
NEUTROPHIL %	median [iqr]	47.5 [14.9, 56.2]	53.0 [46.4, 59.6]	0.037
LYMPHOCYTE %	median [iqr]	37.9 [21.1, 62.7]	34.2 [24.2, 38.9]	0.134
MONOCYTE %	median [iqr]	2.8 [1.8, 5.7]	5.0 [4.3, 6.2]	<0.01
EOSINOPHIL %	median [iqr]	0.8 [0.3, 2.9]	3.2 [2.0, 6.9]	<0.01
BASOPHIL %	median [iqr]	0.6 [0.3, 1.5]	0.6 [0.3, 0.8]	0.429

LUC %	median [iqr]	7.5 [3.8, 17.8]	3.0 [2.2, 3.8]	<0.01
NEUTROPHILABS (ANC)	median [iqr]	1.9 [0.5, 4.4]	3.5 [2.5, 4.3]	<0.01
LYMPHOCYTE ABS	median [iqr]	1.5 [0.9, 4.9]	2.0 [1.5, 2.7]	0.251
MONOCYTE ABS	median [iqr]	0.2 [0.1, 0.3]	0.4 [0.3, 0.4]	<0.01
EOSINOPHIL ABS	median [iqr]	0.0 [0.0, 0.2]	0.2 [0.1, 0.4]	<0.01
BASOPHIL ABS	median [iqr]	0.0 [0.0, 0.1]	0.0 [0.0, 0.1]	0.59
LUCABS	median [iqr]	0.3 [0.2, 1.0]	0.2 [0.1, 0.3]	0.014

There was a significant difference between the CBC parameters at the time of relapse with reduced hemoglobin ($p=0.015$), RBC count ($p=0.001$), platelet count ($p<0.001$), absolute neutrophil count ($p<0.01$), % neutrophil ($p=0.037$), % monocyte ($p<0.01$), % eosinophil ($p<0.01$), % large unstained cells ($p<0.01$).

Discussion:.Prediction of relapse in pediatric B-ALL was the main aim of our study, so that clinical intervention could be done to improve the disease relapse related survival.

Many studies are done to identify risk factors which can predict relapse. Risk factors such as age ≥ 10 years, peripheral blood WBC count >100 X 10^9/L at diagnosis, time of agranulocytopenia ≤ 7days, peripheral blood blast count at diagnosis and at day 8 (prednisone response), Platelet count at diagnosis, risk stratification, MRD at day 15 and day 33, role of NK cells, cytogenetic gene fusions like BCR-ABL, TEL-AML1 and E2A-PBX1 etc were studied by various groups[4]. However, there is no clear indicator that can indicate intimidate impending relapse in the coming few days or months, allowing clinical intervention to improve the disease relapse related survival. This is the first study where we have systematically studied CBC parameters of B-ALL patients.

In current clinical practice B-ALL patients are closely monitored for clinical features and CBC investigation at regular interval. Our aim was to conduct a systematic study of the CBC parameters and their relevance to predict or identify patients with a probability of immediate relapse. In our study, we included 90 B-ALL patients in which 30 cases were relapse and 60 cases were non-relapse. Median age was 7.5 years and 5.0 years in relapse and non-relapse group respectively. Male patients predominated in both the groups.

Seventeen haematological parameters of B-ALL patients were studied, from diagnosis till either relapse (in relapse group) or 2 years follow-up/last follow-up (in non-relapse group). We selected 3 time points for relapse group namely, relapse time-point, 1-3 months before relapse and 3-6 months before relapse, as our aim was to find out parameter which will predict impending relapse. Similarly for non-relapse group we selected time point 2years follow up after initiation of therapy or last follow-up. We compared the three time-points of relapse group with that of non-relapse group. In comparison between time point of 1-3 months before relapse in relapse group and 2years/last follow-up in non-relapse group, Platelet parameter showed significant p-value of 0.048, AUC 0.629 and cut off value of 340 (which was not promising).

With median platelet count of 244 X 10^9/L, relative risk was 1.462 (0.982, 2.174) with p-value 0.0612 (near to significance). Thus it showed that risk of getting relapse increases by 46.2% in patients with platelet count < 244 X 10^9/L as compared to platelet count ≥ 244 X 10^9/L.

No parameter was significant when compared between the time point of 3-6 months before relapse in relapse group and 2years/last follow up in non-relapse group. However, relapse time point showed significant p- value for many parameters like reduced hemoglobin (p=0.015), RBC count (p =0.001), platelet count (p <0.001), absolute neutrophil count (p <0.01), % neutrophil (p =0.037), % monocyte (p <0.01), % eosinophil (p <0.01), % large unstained cells (p <0.01), absolute monocyte count (p <0.01) and absolute eosinophil count (p <0.01), large unstained cells (p <0.014).

The main limitation of our study was the small cohort size and retrospective design, which are susceptible to selection bias in data analysis and might have affected the accuracy of results. Hence these results need to be observed in a large cohort.

Conclusion: Thus, we concluded that platelet count have a high potential to predict impending relapse and provide a basis to investigate further for confirmation with ancillary tests. CBC testing is cheap and available in all laboratories. Hence it can be part of routine close monitoring of B-ALL patients.

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All the staffs of Hematopathology laboratory and Pediatric Hemato-lymphoid Department, TMH and ACTREC.

Competing interests statement:

The authors declare no competing interests.

Abbreviations:

ABS- Absolute (count)

ACTREC - Advance Centre for Treatment, Research and Education in Cancer

AUC - Area under the Curve

BCR-ABL- Breakpoint cluster region (BCR) and Abelson proto-oncogene (ABL)

BM – Bone marrow

CBC - Complete Blood Count

CNS - Central nervous system

EMR – Electronic Medical Record

Hb – Hemoglobin

IQR - Interquartile Range

LUC- Large unstained cells

MCV – Mean cell volume

NK- Natural killer cells

RBC- Red blood cell

TMC - Tata Memorial Centre

TMH - Tata Memorial Hospital

WBC- White Blood Cell

Author contributions:

Leena Fernandes collected and analyzed the data and wrote the paper. Dr.Prashant Tembhare participated in the writing. Dr. Chetan Dhamane, Dr. Mahendra Kumar Verma, Dr. Rachna, Dr Guarav Narula, Dr. Sripad Banavali, Dr. Nirmlya Roy Moulik, Dr. Shyam Srinivasan, Dr. P G Subramanian, Dr. Sumeet Gujral, Dr. Girish Chinnaswomy, Dr. Nikhil Patkar, Dr. Gaurav Chatterjee, Dr. Sweta Rajpal and Dr. Prashant Tembhare assisted in the design of this study.

Mrs. Sadhana Kannan and Ms Priti Nhavi took the responsible for the integrity of the data and the accuracy of the data analysis. All authors critically revised the manuscript.

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