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RESEARCH ARTICLE

# PERIPHERAL BLOOD COUNT RECOVERY TIME COURSE DURING INDUCTION TREATMENT FOR ACUTE LYMPHOBLASTIC LEUKEMIA IN CHILDREN

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## Abstract

**Background**: In recent years, the survival rate of pediatric ALL patients has increased to almost 90%, particularly for individuals with favorable prognoses. This success is mostly attributable to the use of risk-adapted medication, enhanced supportive care, and adjustments to therapy based on each patient's unique pharmacodynamics and pharmacogenomics. This research investigates ALL patients' response to induction chemotherapy, focusing on changes in peripheral blood cell counts and hematological markers, to predict therapeutic outcomes and provide a practical prognostic parameter.

**Methods:** This study involved 100 under 15 year-old patients with newly diagnosed ALL treated in pediatric leukemia units at Kuwait Hospital, Sana'a. Blood markers were collected and analyzed using Epi Info statistical program version 6. The study followed the French, American, and British classifications of pediatric leukemia. Participants were informed of the study's goals and advantages, and their participation was optional.

**Results:** The majority of patients were aged 5-9 years, with a mean age of 6.9 years. Hemoglobin levels were measured before and after treatment, with the mean level being 8.8 mg/dL before and 10.8 mg/dL after treatment. Severe anemia was reported in 10% of patients before treatment and decreased to 2% after treatment. PCV levels were also measured before and after treatment, with the mean PCV level being below normal in 66% of patients before induction chemotherapy but improving to 20% after treatment. The mean RBC count before treatment was 2.9 cells × $10^6$/µl, but improved to 3.8 cells × $10^6$/µl after induction chemotherapy. The study found that over 50% of patients had iron deficiency anemia before and after induction chemotherapy, with a mean neutrophil percentage of 18.2%, lymphocyte percentage of 73.7%, monocyte percentage of 3.8%, and eosinophil percentage of 0.85%.

**Conclusions:** The study reveals that blood cell parameters replenish at different rates during induction chemotherapy, resulting in rapid platelet and slow neutrophil recovery. Changes in blood markers during induction may be prognostic.

**Keywords:** Acute Lymphoblastic Leukemia (ALL), children, induction chemotherapy, peripheral blood count, Sana'a city, Yemen.

## INTRODUCTION

Seventy five to 80% of cases of acute leukemia in children are caused by Acute Lymphoblastic Leukemia (ALL), the most common cancer in this age range. In children under the age of 15, the incidence of childhood ALL is 3.4–5 cases per 100,000. Although it affects children of all ages, the incidence is highest in the two to five age range, with a small male predominance[1]. Because ALL is a diverse disease, distinct subtypes have varying outcomes and differ in terms of biological, cellular, and molecular features, response to therapy, and risk of relapse[2]. In recent years, the survival rate of pediatric ALL patients have increased to almost 90%, particularly for individuals with favorable prognoses. This success is mostly

attributable to the use of risk-adapted medication, enhanced supportive care, and adjustments to therapy based on each patient's unique pharmacodynamics and pharmacogenomics[2,3]. A variety of clinical, biological, and genetic factors, including age and gender, the number of white blood cells (WBC) at diagnosis, immunophenotypic, cytogenetic, and molecular traits, as well as the early medullar response to induction therapy, are used to stratify patients into risk groups[4-6]. The most important predictor of outcome for people with ALL at this time is their early response to therapy, which is assessed by their minimal residual disease (MRD) at the conclusion of induction[7].

Numerous factors, including pretreatment and post treatment parameters, affect the prognosis of ALL[4]. Accurate clinical prognostic analysis and more focused, tailored treatment will lower recurrence and increase OS in the early phases of ALL diagnosis and treatment. Changes in peripheral blood cell counts in ALL patients following induction chemotherapy often indicate the chemo-sensitivity and toxicity of the treatment *in vivo*. Therefore, it would be important to investigate further if peripheral blood alterations following ALL induction may accurately predict the therapeutic impact of chemotherapy.

Although leukemia is highly treatable in the developed world, little is known about the disease's present state in Yemen in general and the study location in specific. However, Yemen, like the majority of Arab nations, lacks specialist epidemiological registries for this area, which is why it's critical to support, maintain, expand, and deliver pediatric leukemia research. With early diagnosis and appropriate treatment targeted at improving survival and avoiding potential effects, the objective is to have a bigger impact on public health. The few available studies on cancer in Yemen indicate that leukemia (33.1%), lymphoma (31.5%), and central nervous system tumors (7.2%) and bone tumors (5.2%) are the most prevalent cancer types among Yemeni adults and children[8-13].

The objective of this research is to investigate how ALL patients respond to induction chemotherapy by identifying changes in peripheral blood cell counts and other hematological markers during the initial round of induction chemotherapy. Additionally, the study aims to predict ALL patients' therapeutic outcomes based on changes in peripheral blood cell counts and to offer a practical and uncomplicated parameter for the clinical prognostic assessment of ALL.

## SUBJECTS AND METHODS

**Study design:** Based on a sample of 100 patients under the age of 15 who had recently been diagnosed with ALL and were receiving selected treatment in the pediatric leukemia units of Kuwait Hospital in Sana'a, this prospective study was conducted. Over the course of a year, from January 1, 2023, to December 31, 2023, the mass diagnostic and histological diagnosis was developed in accordance with the French, American, and British classifications of pediatric leukemia. Pediatric leukemia units at Kuwait Hospital is public referral hospital providing treatment of childhood leukemia in Sana'a city. The observed blood markers included: Haemoglobin level, PCV, RBCs counts, WBCs counts, platelets counts, WBCs differential counts, MCV, MCH, MCHC, and RDW.

**Data collection:** Individual information, such as clinical information, demographic information, and test results, were gathered using a pre-design questionnaire.

**Statistical analysis:** The data was analyzed using the Epi Info statistical tool version 6 (CDC, Atlanta, USA). When the quantitative data was normally distributed, it was expressed as mean values or standard deviation (SD). applying percentages to the qualitative data.

**Ethical consideration:** Prior to gathering data, the institution's ethical review committee gave its approval. All participants or/and their guardians received an explanation of the study's goals and advantages prior to involvement, and their verbal informed agreement was obtained. Participants and their families were also told that their participation was optional and that they might decline it without giving a reason.

## RESULTS

The study analyzed the age and sex distribution of pediatric leukemia patients at Al-Kuwait University Hospital in Sana'a City, Yemen. The majority of patients were aged 5-9 years, with a mean age of 6.9 years. Hemoglobin levels were measured before and after treatment, with the mean level being 8.8 mg/dL before treatment and 10.8 mg/dL after treatment.

**Table 1: Sex and age distribution of leukemia children patients in Al-Kuwait Hospital, Sana'a city, Yemen.**

| Characters | N (%) |
|---|---|
| Sex | |
| Male | 51 (51) |
| Female | 49 (49) |
| Age groups (years) | |
| Less than 5 years | 27 (27 ) |
| 5-9 years | 47 (47 ) |
| ≥10 years | 26 (26 ) |
| Total | 100 (100) |
| Mean age | 6.9 years |
| SD | 3.8 years |
| Median | 7 years |
| Mode | 5 years |
| Min - Max | 9 months - 14 years |

The normal Hb level for children is 11.9 to 15 g/dl; that for male and females. PCV levels were also measured before and after treatment. The mean PCV level was below normal in 66% of patients before induction chemotherapy, but improved to 20% after treatment. The mean RBC counts before treatment was 2.9 cells ×106/µl, but improved to 3.8 cells×106/µl after induction chemotherapy (Table 4). A normal RBC count would be around: children – 4.0 to 5.5x 10*12/L. A normal WBC count would be around: children (4.5 to 11.0 × 109/L. The mean white blood cell count was 29.5 cells × $10^9$/L with an SD of 23.6 and ranged from 2.4 to 97 cells×$10^9$/L before induction chemotherapy. After induction chemotherapy, the mean white blood

cell count decreased to 3.9 cells×$10^9$/L with an SD of 2.4 and ranged from 0.3 to 10.7 cells×$10^9$/L (Table 5). The mean neutrophils percentage was 18.2% with an SD of 23.7 and ranged from 0.0 to 85% before induction chemotherapy.

**Table 2: HGB level of children leukemia patients before and after treatment.**

| Characters | Before N (%) | After |
|---|---|---|
| HGB (mg/dL ) | | |
| Less than 5 | 10 (10 ) | 2 (2) |
| 5- 8 | 26 (26 ) | 6 (6) |
| 8.1 -11 | 48 ( 48) | 40 (40) |
| ≥11.1 | 16 ( 16 ) | 52 (52) |
| Total | 100 (100) | 100 (100) |
| Mean | 8.8 | 10.8 |
| SD | 2.5 | 1.8 |
| Median | 9.2 | 11.2 |
| Mode | 6.5 | 11.4 |
| Min - Max | 3.8 – 15.2 | 4.7 - 14 |

After induction chemotherapy, the mean neutrophil count increased to 34% with a standard deviation of 23.3% and ranged from 0.7 to 85% (Table 6). The mean lymphocytes percentage was 73.7% with an SD of 26.3 and ranged from 9.3 to 99% before induction chemotherapy. After induction chemotherapy, the mean lymphocytes count decreased to 55.5% with a standard deviation of 23.6% and ranged from 13 to 96% (Table 7). The mean monocytes percentage was 3.8% with an SD of 6.2 and ranged from 0 to 34% before induction chemotherapy. After induction chemotherapy, the mean monocytes count to 7.6% with a standard deviation of 7.9% and ranged from 0.1 to 35% (Table 8).

**Table 3: PCV level of children leukemia patients before and after treatment.**

| Characters | Before N (%) | After N (%) |
|---|---|---|
| PCV | | |
| Less than 30.0 | 66 (66 ) | 20 (20) |
| 30 – 40 | 30 (30 ) | 66 (66) |
| >40.0 | 4 (4 ) | 14 (14) |
| Total | 100 (100) | 100 (100) |
| Mean | 26.2 | 34.5 |
| SD | 7.6 | 5.5 |
| Median | 27 | 35.4 |
| Mode | 27 | 36 |
| Min - Max | 10.3 – 48 | 23-45 |

Normal levels of PCV in children range from 30% to 44%.

The mean Eosinophil percentage was 0.85% with an SD of 1.9 and ranged from 0 to 9.4% before induction chemotherapy. After induction chemotherapy, the mean Eosinophil count was 1.5% with a standard deviation of 1.9% and ranged from 0.0 to 7.3% ( Table 9). The mean MCV was 78 fl with SD equal to 15.2fl, and the MCV ranged from 10 fl to 96 fl before induction chemotherapy. After induction chemotherapy the mean MCV was 81.6 fl with SD equal to 11.6 fl, and the MCV ranged from 10 fl to 97 (Table 11). Below 80 fl (femtoliters), they will likely develop or have microcytic anemia. Alternatively, if their MCV levels are greater than 100 fl, they could experience macrocytic anemia. The mean MCH was 27.3 picograms per cell with SD equal to 3.7, and the MCH ranged from 22 to 42 before induction chemotherapy. After induction chemotherapy the mean MCH was 26.1 with SD equal to 2.3, and the MCH ranged from 19 fl to 32. More of 50% of the patients had less than 27 p/cell before and after inducing chemotherapy indicating iron deficiency anemia while 14% before treatment had 27-28 p/cell and 2% after induction chemotherapy indicating anemia due to low levels of folic acid or vitamin B12 (Table 12).

**Table 4: Red blood cell counts of children leukemia patients before and after treatment ($10^6$/µL).**

| Characters | Before N (%) | After N (%) |
|---|---|---|
| RBC (cell x $10^6$/µL ) | | |
| Less than 2.0 | 12 (12) | 0 (0) |
| 2 – 3.9 | 64 (64) | 42 (42) |
| ≥4.0 | 24 (24) | 58 (58) |
| Total | 100 (100) | |
| Mean | 2.9 | 3.8 |
| SD | 0.95 | 0.71 |
| Median | 3.01 | 3.0 |
| Mode | 2 | 4.02 |
| Min - Max | 2.01- 5.1 | 2.1- 5.2 |

Before receiving induction chemotherapy, the MCHC varied from 29 to 46 g/dl, with a mean of 33.3 g/dl and an SD of 3.6. Following induction chemotherapy, the MCHC varied from 28 to 34, with a mean of 31.2 and a standard deviation of 1.2. After starting chemotherapy, more than 60% of the patients had anemia (less than 32 g/dl), whereas 34% had this level prior to treatment (Table 13). A typical MCHC result is 32–36 grams/deciliter (g/dL) or 320–360 grams per liter (g/L), although this may vary depending on the lab. Levels outside this range can indicate anemia.

**Table 5: White blood cell counts of children leukemia patients before and after induction chemotherapy ($10^9$/L).**

| Characters | Before N (%) | After N (%) |
|---|---|---|
| WBC (cell x $10^9$/L ) | | |
| Less than 2.0 | 0 (0 ) | 20 (20) |
| 2 – 4.4 | 14 (14) | 48 (48) |
| ≥4.5 | 86 (86) | 32 (32) |
| Total | 100 (100) | |
| Mean | 29.5 | 3.9 |
| SD | 23.6 | 2.4 |
| Median | 24.3 | 3.5 |
| Mode | 25 | 2.4 |
| Min - Max | 2.4 -97 | 0.3 – 10.7 |

Prior to starting chemotherapy, the RDW for used patients ranged from 12 to 28%, with a mean of 16.5% and a standard deviation of 3.3%. The mean following chemotherapy induction was 16.7%, with a standard deviation of 2.9% and a range of 13 to 26% (Table 14).

## DISCUSSION

In this study, we report a cohort of 100 children with acute lymphocytic leukemia who recovered from peripheral leukopenia following the start of induction chemotherapy. Obtained results indicate that recovery from severe neutropenia happens more slowly, but recovery from thrombocytopenia and anemia needing blood transfusion can be anticipated within two weeks. Once partial recovery occurs, the count returns to normal soon after (Table 5, and Table 6).

**Table 6: Neutrophils counts of children leukemia patients before and after treatment (%).**

| Characters | Before N (%) | After N (%) |
|---|---|---|
| Less than 2.0% | 24 (24) | 4 (4) |
| 2 – 10 | 30 (30) | 22 (22) |
| 11-39 | 22 (22) | 32 (32) |
| ≥40 | 24 (24) | 42 (42) |
| Total | 100 (100) | |
| Mean | 18.2 | 34 |
| SD | 23.7 | 23.3 |
| Median | 9 | 32 |
| Mode | 1 | 5 |
| Min - Max | 0.0 - 85 | 0.7 – 85 |

Platelet counts (PLCs) of pediatric leukemia patients in the current study are shown. Before treatment, the platelet counts of the patients ranged from 7 to 423 cells per microliter (mcL), with a mean of 67.7 cells per microliter (mcL) and SD of 86 cells per milliliter. After treatment, the count ranged from 13 to 470 cells per microliter (mcL), and the mean improved to 235 cells per microliter with an SD of 178 cells per microliter (mcL) (Table 15). This result indicated rapid recovery with low morbidity, and was associated with good response to treatment, and this result is consistent with what Grunnan *et al.*, reported in his study[14].

**Table 7: Lymphocytes counts of children leukemia patients before and after treatment (%).**

| Characters | Before N (%) | After N (%) |
|---|---|---|
| Less than 40 % | 14 (14) | 32 (32) |
| 40 – 60 | 8 (8 ) | 24 (24) |
| 61-80 | 22 (22) | 24 (24) |
| ≥81 | 56 (56) | 20 (20) |
| Total | 100 (100) | |
| Mean | 73.7 | 55.5 |
| SD | 26.3 | 23.6 |
| Median | 84.6 | 56.2 |
| Mode | 71 | 72 |
| Min - Max | 9.3 - 99 | 13-96 |

In the current study, the mean hemoglobin level in pediatric leukemia patients before induction chemotherapy was 8.8 mg/dL, and after 2 weeks of induction chemotherapy the values changed to the mean of 10.8 mg. /dL and severe anemia (less than 5 mg/dL) was reported in 10% before treatment and decreased to 2% after treatment. This distinctive pattern shows that neutrophil regeneration was somewhat delayed, but PLC regeneration occurred rather quickly, followed by Hb recovery (Table 2, Table 4, and Table 15). Partial recovery is the most significant factor in terms of morbidity. According to the pattern of recovery, the risk of infection or bacteremia frequently lasts the entire induction period, while bleeding or anemia necessitating transfusion therapy mostly happens in the first two weeks. All blood cells should fully recover after a few weeks, assuming some recovery has taken place[14-16].

**Table 8: Monocyte counts of children leukemia patients before and after treatment (%).**

| Characters | Before N (%) | After N (%) |
|---|---|---|
| Less than 2 % | 62 (62) | 28 (28) |
| 2-8 | 20 (20) | 38 (38) |
| >8 | 18 (18) | 34 (34) |
| Total | 100 (100) | |
| Mean | 3.8 | 7.6 |
| SD | 6.2 | 7.9 |
| Median | 1.2 | 5 |
| Mode | 0.1 | 0.1 |
| Min - Max | 0-34 | 0.1-35 |

Prior to induction chemotherapy, the white blood cell count varied from 2.4 to 97 cells $\times 10^9$/L, with a mean of 29.5 cells$\times 10^9$/L and an SD of 23.6. Following induction chemotherapy, the range of the mean white blood cell count was between 0.3 and 10.7 cells $\times$ $10^9$/L, and it was 3.9 cells $\times 10^9$/L with an SD of 2.4. This suggests a shorter duration of severe anemia and severe neutropenia together with an early marrow recovery.

**Table 9: Eosinophil counts of children leukemia patients before and after treatment (%).**

| Characters | Before N (%) | After N (%) |
|---|---|---|
| Less than 1 % | 80 ( 80) | 52 (52 ) |
| 1-6 | 14 (14) | 40 (40 ) |
| >6 | 6 (6) | 8 (8 ) |
| Total | 100 (100) | 100 (100) |
| Mean | 0.85 | 1.5 |
| SD | 1.9 | 1.9 |
| Median | 0.1 | 0.7 |
| Mode | 0.0 | 0.2 |
| Min - Max | 0 - 9.4 | 0 - 7.3 |

Consequently, there was less morbidity in terms of the requirement for blood products and antibiotic therapy. Prior to induction chemotherapy, the mean percentage of lymphocytes in the current study ranged from 9.3 to 99%, with a standard deviation of 26.3. Following induction chemotherapy, the range of 13 to 96% was observed in the mean lymphocyte count. Numerous studies conducted in recent years have demonstrated the predictive importance of the lymphocyte counts at the time of induction. The majority of youngsters exhibit a startling pattern, with lymphopenia developing by the middle of induction and lymphocyte recovery by the conclusion of induction. In 2008, De Angulo *et al.*, discovered that a very low lymphocyte nadir, ALC-15 < 0.35/nL, was a robust and independent predictor of a high event risk in children and adolescents with ALL and AML[17].

**Table 10: Basophile counts of children leukemia patients before and after treatment (%).**

| Characters | Before N (%) | After N (%) |
|---|---|---|
| Less than 1 % | 84 (84) | 72 (72) |
| 1-3 | 6 ( 6) | 20 ( 20) |
| >3 | 10 ( 10) | 10 (10) |
| Total | 100 (100) | 100 (100) |
| Mean | 0.81 | 1.2 |
| SD | 1.7 | 1.9 |
| Median | 0.1 | 0.6 |
| Mode | 0.0 | 0.3 |
| Min - Max | 0 - 7 | 0 - 9.7 |

**Table 11: MCV level of children leukemia patients before and after treatment.**

| Characters | Before N (%) | After N (%) |
|---|---|---|
| MCV /fl (Mean corpuscular volume/femtoleter | | |
| Less than 80 | 42 (42) | 26 (26) |
| 80-84 | 34 (34 ) | 34 (34) |
| 85-89 | 12 (12) | 30 (30) |
| >89 | 12 (12) | 10 (10) |
| Total | 100 (100) | 100 (100) |
| Mean | 78 | 81.6 |
| SD | 15.2 | 11.6 |
| Median | 80 | 82 |
| Mode | 83 | 80 |
| Min - Max | 10 - 96 | 10 - 97 |

Since then, two Chinese studies using ratios of mid-induction aleukemic leukemia cutis (ALC) to initial ALC have shown that a low ratio is correlated with a high Minimal residual disease (MRD)[18] and linked to a worse event free survival[19]. Low counts at the conclusion of induction are a risk factor, and the subsequent recovery of lymphocytes may also be predictive.

**Table 12: MCH level of children leukemia patients before and after treatment.**

| Characters | Before N (%) | After N (%) |
|---|---|---|
| MCH (mean corpuscular hemoglobin/picograms per cell) | | |
| Less than 27 | 54 ( 54) | 56 (56) |
| 27-28 | 14 ( 14 ) | 32 (32) |
| 29-31 | 18 ( 18) | 10 (10) |
| >31 | 14 (14) | 2 (2) |
| Total | 100 (100) | 100 |
| Mean | 27.3 | 26.1 |
| SD | 3.7 | 2.3 |
| Median | 26 | 25 |
| Mode | 26 | 25 |
| Min - Max | 22 - 42 | 19 - 32 |

The normal range for MCH is 27 to 31 picograms per cell. Anything above or below that may indicate an underlying condition, usually a type of anemia. Low levels of MCH can indicate iron-deficiency anemia while high levels of MCH

Research has demonstrated that ALC-29 < 0.35/nL is linked to a low rate of survival[20], that ALC > 0.5/nL at the conclusion of induction represents a higher rate of survival in children who do not have MRD[21], and that ALC-29 >1.5/nL represents a higher rate of relapse-free survival in patients with MRD[22]. However, a later investigation using a different ethnic group treated with a seven drug induction was unable to confirm the latter conclusion[23].

**Table 13: MCHC level of children leukemia patients before and after treatment.**

| Characters | Before N (%) | After N (%) |
|---|---|---|
| MCHC g/dl | | |
| Less than 32 | 34 (34) | 62 (62) |
| 32-33.9 | 32 (3) | 32 (32) |
| >33.9 | 34 (34) | 6 (6) |
| Total | 100 (100) | 100 (100) |
| Mean | 33.3 | 31.2 |
| SD | 3.6 | 1.2 |
| Median | 32 | 31 |
| Mode | 31 | 31 |
| Min - Max | 29 – 46 | 28 -34 |

**Table 14: RDW level of children leukemia patients before and after treatment.**

| Characters | Before N (%) | After N (%) |
|---|---|---|
| RDW percent | | |
| Less than 12 | 2 (2 ) | 0 (0) |
| 12-15 | 46 (46 ) | 40 (40) |
| 15.1-16 | 14 (14) | 22 (22) |
| >16 | 38 ( 38) | 38 (38) |
| Total | 100 (100) | 100 (100) |
| Mean | 16.5 | 16.7 |
| SD | 3.3 | 2.9 |
| Median | 16 | 16 |
| Mode | 14 | 16 |
| Min - Max | 12 – 28 | 13 – 26 |

**Table 15: Platelets counts of children leukemia patients before and after treatment.**

| Characters | Before N (%) | After N (%) |
|---|---|---|
| Per microliter x$10^3$ | | |
| Less than 150 | 90 (90 ) | 42 (42) |
| 150-450 | 10 (10) | 49 (49) |
| >450 | 0 ( 00) | 9 (9) |
| Total | 100 (100) | 100 |
| Mean | 67.7 | 235 |
| SD | 86 | 178 |
| Median | 37 | 227 |
| Mode | 9 | 47 |
| Min - Max | 7 – 423 | 13 - 470 |

A normal platelet count ranges from 150,000 to 450,000 platelets per microliter of blood. Having more than 450,000 platelets is a condition called thrombocytosis; having less than 150,000 is known as thrombocytopenia.

We can track changes in peripheral blood cell counts in patients with ALL in order to determine the prognosis of the condition at the outset of clinical treatment and to quickly develop tailored treatment plans and programs to enhance the prognosis of ALL patients. Day 14 of induction chemotherapy for ALL patients shows alterations in the peripheral blood.

**Limitation of the study**

This is only a single center retrospective study, thus the multicenter study is necessary to corroborate the findings. Nevertheless, it is a practical and simple prognostic measure to assess the effectiveness of induction chemotherapy in ALL patients.

## CONCLUSIONS

This retrospective analysis concluded that distinct blood cell counts refill during induction chemotherapy, resulting in varying rates of platelet recovery and neutrophil recovery. Complete recovery raises the possibility of a positive response to chemotherapy, partial recovery shows early bone marrow regeneration with a low prevalence of illness, and PLC might be a helpful clinical marker. Furthermore, current research supports newer data demonstrating that blood marker variations throughout induction can have predictive significance, with a very low nadir at day 15 indicating a poor response to therapy. To find out if variations in peripheral counts during induction contribute to treatment stratification, more research is required.

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## DATA AVILIABILITY

The data will be available to anyone upon request from the corresponding author.

## CONFLICT OF INTEREST

None to declare.

## AUTHOR'S CONTRIBUTION

**El-Zine MAY:** writing original draft, methodology, investigation. **Hamayun R:** conceptualization, data interpretation, formal analysis. **Ali MAA:** writing, review and editing, methodology, data curation. Final manuscript was read and approved by all authors.

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