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Interleukin 6 and interleukin-1β levels association with haematological and biochemical findings in patients with chronic myeloid leukaemia

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Abstract

Numerous pro-inflammatory cytokines play a role in the Chronic Myeloid Leukaemia (CML) etiology. The current study evaluated the levels of IL-6 and IL-1β in different phases of CML compared to healthy controls. Additionally, we explored their associations with a range of haematological, biochemical, and coagulation parameters, which are essential for monitoring their treatment. The study comprised 55 patients of CML, of which 34 (62%) were male and 21 (38%) were female. The enzyme-linked immunosorbent assay was used to measure the levels of IL-6 and IL-1β. A significant difference was observed in IL-6 levels between the blast phase and controls. However, IL-1β levels did not significantly differ among disease stages and controls. IL-6 and IL-1β levels were higher in atypical CML forms, with significant differences observed only in IL-6 levels. Parameters like Red Blood Cell Distribution Width, spleen size, uric acid, LDH, and prothrombin time increased with disease progression, while APTT levels remained within normal range. Positive significant correlations were found between IL-6, Mean Corpuscular Volume, LDH, and uric acid. Understanding these correlations is crucial for managing CML patients and devising appropriate treatment strategies. Further research is needed to understand the clinical implications and utility of these correlations in patient management.

Keywords: Interleukin-6, Interleukin-β, Chronic Myeloid Leukaemia.

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1. Introduction

Chronic myeloid leukaemia (CML) is a condition characterized by the abnormal fusion of genes due to a specific translocation of chromosomes 9 and 22, also called as Philadelphia (Ph) chromosome. This fusion leads to the formation of the BCR-ABL gene [1]. The World Health Organization (WHO) classifies CML into three stages based on its progression and severity: the chronic phase (CP), which is the initial stage with fewer than 10% blast cells, the accelerated phase (AP) or progressive phase with 10% to 19% blast cells, and the blast phase (BP) where blast cells make up 20% or >20 % blasts [2]. The strong association between interleukins and cancer is reflected by high levels of interleukins in the tumor environment. Interleukin-6 (IL-6) is a multi-poietic cytokine able to stimulate the growth and differentiation of immune cells and also exerts many effects on cancer cells. Apart from its role in hematopoiesis and possessing anti-inflammatory properties, IL-6 plays a crucial role in CML, where it modulates the activity of leukemic stem cells, thereby promoting disease progression [3]. IL-6 are notably elevated in CML patients at the time of diagnosis compared to healthy individuals, with persistently high IL-6 levels serving as an indicator of poor response to chemotherapy [4]. Pro inflammatory cytokines in CML, like IL-6 and IL-1β have been studied in different stages and it is regarded as a prominent target for clinical interventions. Patients with CML have high levels of biologically active IL-1β. Various investigations have uncovered the role of IL-1 β in human stem cells and myeloid cell homeostasis [5]. When compared to the chronic phase, advanced blast phase shows higher levels of IL-1β, which is linked to blast proliferation in the bone marrow and is associated to a less favourable outcome and shorter patient survival [6]. The clinical and haematological markers of CML are important tools used for diagnosis, clinical staging, prognosis and treatment management of the disease. The red blood cell distribution

width (RDW) is one of the marker used to classify CML-CP patients based on how likely they are responding to a given treatment. This kind of stratification may make treatment planning easier. Elevated RDW values were linked to splenomegaly, lower haemoglobin levels, female sex, higher WBC counts, and higher blast cells. This stratification based on RDW values provides a practical approach to enhance treatment planning and improve patient outcomes [7]. Continuous biochemical monitoring of uric acid concentration and serum lactate dehydrogenase (LDH) activity can play an important role in monitoring the prognostic aspect of the disease. The haemostatic parameters are significantly disturbed in CML and correlate positively with the progression of the disease [8]. Complete laboratory workup including haematological, biochemical evaluation of each CML patient becomes essential at the time of early diagnosis, therapy and follow up [9]. In our study, we investigated the levels of IL-6 and IL-1β across various phases of CML in comparison with healthy controls. Additionally, we explored the correlation between these inflammatory markers and a range of haematological, biochemical, and coagulation parameters, which serve as crucial indicators for monitoring the prognosis of leukemia both during and after treatment.

2. Materials and methods

KS Hegde Charitable Hospital and Yenepoya Hospital in Mangaluru, Karnataka, India, conducted this descriptive study based on hospital records from 2021 to 2023. Fifty five clinically diagnosed CML patients were referred to the Genetic lab (KS Hegde Medical Academy, Mangalore, Karnataka, India). The ethical clearance for this study was obtained from the central ethics committee, NITTE (Deemed to be University) (Ref: NU/CEC/2021/168). Written informed consent was taken from each patient. All the baseline characteristics haematological, biochemical parameters were collected for analysis. About 4ml of the blood was collected in the EDTA vacutainer. Plasma was extracted, and stored at -80^{0}C until further use. The levels of IL-6 and IL-1β were quantitatively determined in cases and controls using Enzyme-Linked Immunosorbent Assay (ELISA) Kits (Krishgen Biosystems, India). The tests were carried out according to the manual instruction. Absorbance was measured with the multimode microplate ELISA reader (Spark Tecan, Switzerland) [10].

2.1. Statistical Analysis

The data were analyzed using a two tailed Student's test, the relationship between phases of CML and laboratory parameters was analysed by one way ANOVA. The Pearson's correlation analysis of haematological, biochemical and coagulation parameters with inflammatory cytokines was performed using Graph Pad Prism version 6.04, San Diego, CA, USA.

3. Results

In the present study total, 55 cases of CML were included, consisting of 34 (62%) males and 21 (38%) females. Median age of males was 41(34-57) years and median age of females was 45 years (31-64). The study was conducted for three years. The phase wise distribution of CML patients are as follows,the CP were 40 (72%),AP were 9(16%) and 6 (12%) were in BP.

3.1 IL-6

Plasma IL-6 levels in the healthy control group was 126.1±24.72 pg/mL. The IL-6 levels in different stages of CML was 191.6±38.84 in the CP, 230.4±56.74 in the AP, and 498.5±142.2 in the BP. Furthermore, in comparison to the control, the results were highly elevated. Moreover, a statistically significant difference ($p<0.05$) was seen between BP and control (Fig:1 A).

3.2 IL-1β

In the healthy group, the plasma IL-1β levels were 25.8±10.75 pg/mL. The concentrations of IL-1β in different stages were 33.44±10.05 pg/mL in the CP, 49.40±15.10 pg/mL in the AP, and 51.37±26.18 pg/mL in the BP, respectively. These levels were elevated across all phases compared to the control. However, no significant differences were observed between the phases and the control group (Fig: 1 B). CML was categorized into typical and atypical subtypes depending on the presence and absence of the Ph chromosome. It was noted that IL-6 and IL-1β levels were significantly higher in the atypical subtype compared to the typical subtype. Specifically, statistical analysis revealed a significant difference in IL-6 levels between typical and atypical forms ($p<0.05$). (Fig: 2 A, B). Various parameters were investigated across different phases of CML, with RDW values showing an elevation as the disease advanced to its terminal stage. Statistical significance was observed between AP and BP ($p<0.05$) (Fig: 3). As the disease progressed to advanced stages, spleen size consistently increased in all patients, indicating significant splenomegaly. Biochemical parameters, including uric acid and LDH levels, showed elevation from the initial phase to later stages of the disease. Statistical significance was observed between the phases of CML for uric acid ($p<0.0001$) and LDH ($p<0.05$), as depicted in Fig: 4 A and B respectively. The haemostatic parameter results are outlined as follows; prothrombin time exceeded the normal range in all phases, while activated partial thromboplastin time remained within normal range across all three phases. However, no statistical significance was observed between these two parameters (table 1). The study revealed significant correlations between the inflammatory cytokine IL-6 and various parameters. There was a positive association was observed between haemoglobin, total leukocyte count, lymphocytes, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), RDW, spleen size, prothrombin time (PT), uric acid levels, and lactate dehydrogenase (LDH) levels. Whereas platelets, basophils, monocytes, blasts, red blood cell count (RBC), and activated partial thromboplastin time (APTT) showed a negative correlation with IL-6 levels. Notably, statistical significance was particularly observed in the correlations between IL-6 MCV, uric acid, and LDH. Similarily IL-1β was correlated with laboratory parameters; positive correlation was seen between total leukocyte count, platelets, lymphocytes, blasts, RBC, MCH, uric acid and LDH. The remaining parameters exhibited a negative correlation, although it was found to be statistically insignificant (table 2).

4. Discussion

In the present study, 55 CML patients were enrolled, comprising of 34 (62%) males and 21 (38%) females. Notably, the prevalence of CML appeared to be more

prominent among males. The median age of males was 41 years and for females it was 45 years. The distribution of patients across disease phases revealed that the majority were in the CP 40 (72%), with smaller proportions in the AP 9(16%) and 6 (12%) in BP. This underscores that a significant portion of the patients were at the early stages of the disease. Comparing our findings with the study conducted by Rajabto et al., [11]. revealed that among 60 patients diagnosed with CML, the median age was 43 years, with 36 (60%) being male and 24 (40%) female aligning closely with our results. Additionally, the predominance of patients presenting in the CP which was closely resembling our own observations. Contrasting our results with those of Tumas et al., [12]. who conducted a study on 601 CML patients in the Lithuanian population, differences emerge, they found a higher median age in both males (62 years) and females (63 years), indicating that CML tends to affect older individuals in their population. Moreover, their study highlighted a higher overall incidence of CML in men, diverging from our observation. This disparity might be attributed due to the differences in population demographics and sample sizes, as our study included a smaller cohort. Notably, when compared to Western literature, our findings challenge some existing notions. Despite the variation, particularly in sample size, our study highlights the need for further research to elucidate the underlying factors contributing to these differences. The study aimed to assess the levels of inflammatory cytokines in CML. The results revealed that plasma levels of IL-6 were elevated across different phases of CML compared to the control group. Moreover, as the disease moved to the advanced stages, with the highest levels was observed in the BP. Notably, a statistically significant difference was observed solely in IL-6 levels between the BP and the control group ($p<0.05$). While no significant differences were noted between the CP and AP. Sharma et al., [13]. reported similar findings indicating an association between CML and increased IL-6 levels. Their study revealed a distinct pattern of serum IL-6 across various phases of CML, with significantly elevated levels compared to the control group. Notably, the highest IL-6 levels were detected during the BP phase of CML. However, similar to our current study, the comparison between CP and AP yielded statistically insignificant results. Matti et al., [14]. conducted a study to assess IL-1β levels in different responders groups that is newly diagnosed, optimal responded, suboptimal responded, failure cytogenetic and advance stages of CML. The newly diagnosed CML patients, exhibited a significant decrease in serum level of IL-1β when compared to the control group. And statistical significant difference was seen between newly diagnosed and control groups. ($p<0.0001$) Patients in the advance disease stage showed a significant increase in levels of IL-1β when compared to the control group($p<0.0001$). In the current study. However our findings diverged from the prior study IL-1β levels were elevated among the different disease stages when compared to the control group and was statistically insignificant. IL-6 and IL-1β levels were higher in the atypical form compared to the typical form of CML, with statistical significance observed only in IL-6 levels $p<0.05$, this study is distinct since no available data is found. The marked elevated levels of IL-6 in comparison to IL-1β suggest a potential association with disease severity and progression among newly diagnosed CML patients. This observation highlights the potential importance of monitoring IL-6 levels as an indicator of disease severity and its involvement in the progression of CML. Consequently, IL-6 emerges as a promising candidate for serving as a prognostic marker in CML, offering valuable insights into disease prognosis and potentially guiding treatment strategies. In our study, laboratory parameters were compared across different stages of CML. RDW values were consistently elevated in all stages, with statistical significance observed between AP and BP. T Li et al., [15]. similarly noted an elevation in RDW when patients of CP transformed to the advance phase in CML. The stratification of CML patients according to their RDW value can be used to determine their prognosis, survival outcomes, and advanced phase. This stratification is beneficial to subsequent treatment. Likewise, in a study conducted by Chang et al., [16]. out of 83 patients, 60 (70.2%) displayed significant splenomegaly, similar to our findings. Furthermore, their study highlighted a progressive increase in spleen size as the disease advanced, indicating a prevalent occurrence of splenomegaly among patients. The biochemical parameters, including uric acid and lactate dehydrogenase (LDH), rised from the initial phase to the later stages of the disease. Statistical significance was observed among the phases of CML for both uric acid and LDH levels. Previous literature studies did not explore the phase wise distribution of uric acid and LDH levels. The haemostatic parameters such as the PT in the CP, AP and BP were elevated beyond the normal range. Whereas the APTT in all the three phases were normal. However no statistical significance was observed between the two parameters. Jain et al., [8].reported a study on 30 patients with CML, 9 (30%) had prolonged APTT and 21 (70%) had normal APTT values. And, 4 (13.3%) patients had prolonged PT and 26 (86.7%) patients had normal PT.The correlation between cancer pathogenesis and inflammation underscores the importance of assessing pro-inflammatory cytokine levels for monitoring disease progression and to detect its role in disease pathogenesis. According to Reynaud et al., [3]. elevated levels of IL-6 and IL-1β have significant role in AML and CML disease progression.In the present study the inflammatory cytokine IL-6 was correlated with different parameters, positive correlation was observed between haemoglobin, total leukocyte count, lymphocytes, MCV, MCH, MCHC, RDW, PT. But only Statistical significance was observed between IL-6 and MCV. Whereas the platelets basophils, monocytes, blasts, RBC and APTT was negatively correlated with IL-6. Anand et al.,[17]. reported that IL-6 serum levels were found to correlate significantly with monocyte counts, blasts and basophil counts, which serve as crucial prognostic indicators. These correlations were statistically significant, with p values indicating significance levels of <0.0001, <0.05, and <0.001 respectively. According to Shatha et al., [4]. findings revealed a positive correlation between IL-6 levels and Body mass index as well as lymphocyte count, with statistical significance ($p<0.01$ and $p<0.001$, respectively).

Parameters	CP N=40	AP N=9	BP N=6	p value
RDW Red blood cell distribution width [11-15%]	19.04±4.20	17.23±3.39	25.97±7.318	<0.05
Spleen size (cm) Massive (≥ 10cm) Moderate(4-9 cm) Mild (1-3 cm)	11.78±6.91	13.18±4.14	17.37±4.67	0.13
Biochemistry parameters				
Uric acid [3.5-7.2mg/dL]	5.34±1.86	7.30±1.07	8.48±1.07	<0.0001
Lactate Dehydrogenase [120 - 246 U/L]	678.3±260.2	775±388	1697±1084	<0.05
Coagulation tests				
Prothrombin time(PT) [11.73-14.6secs]	15.03±1.77	15.47±1.89	16.25±2.18	0.23
Activated Partial Thromboplastin Time (APTT) 26.6-39.13 secs)	35.66±5.16	35.39±5.39	37.13±6.84	0.63

Table 1: Distribution of various parameters in all stages of CML

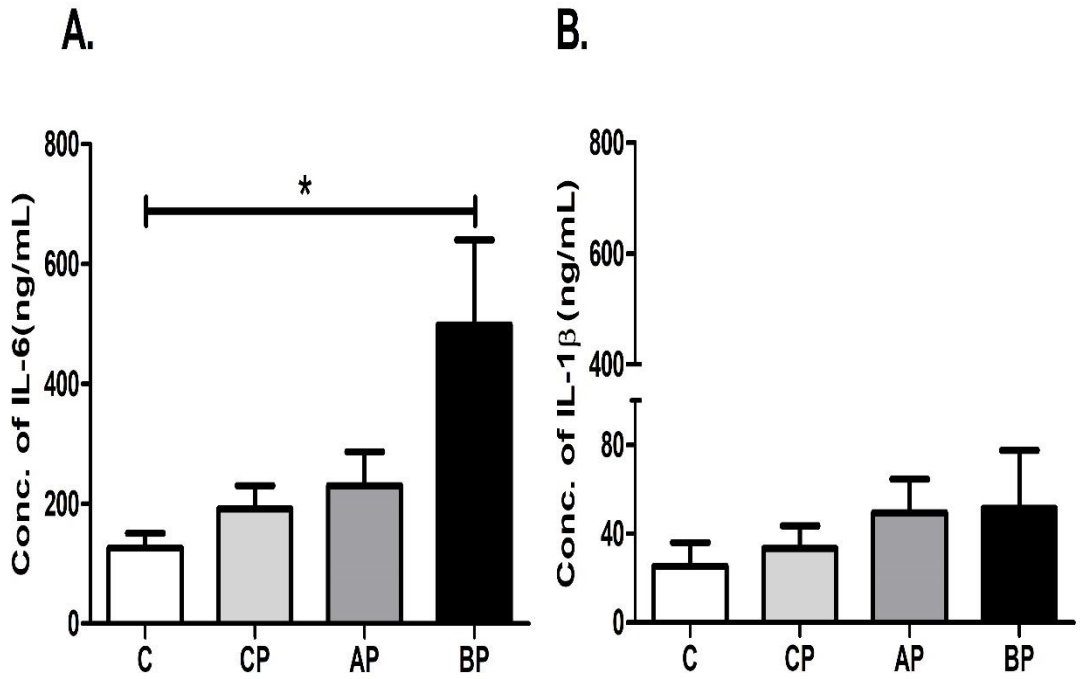

Figure 1: A. IL-6 levels in different phases of CML and Control; B. IL-β levels in different phases of CML and Control

Table 2: Correlation analysis of inflammatory cytokines with haematological, biochemical in CML patients

Parameters	IL-6		IL-1 β	
Haematological	r	p	r	p
Haemoglobin	0.2096	0.1246	-0.08898	0.5183
Total Leukocyte Count	0.03005	0.8276	0.1363	0.3210
Platelets	-0.1813	0.1853	0.09421	0.4939
Basophils	-0.01407	0.9188	-0.1463	0.2864
Monocytes	-0.04808	0.7274	-0.04363	0.7518
Lymphocytes	0.01724	0.9006	0.03548	0.7970
Blast	-0.05180	0.7072	0.02280	0.8688
RBC	-0.1278	0.3526	0.06109	0.6577
MCV	0.2697	<0.05*	-0.00140	0.9919
MCH	0.05316	0.6999	0.04432	0.7480
MCHC	0.01415	0.9183	-0.00676	0.9609
RDW	0.1239	0.3674	-0.0383	0.7810
Spleen size	0.2096	0.1246	-0.08898	0.5183
Coagulation test				
APTT	-0.08414	0.5414	-0.1354	0.3244
PT	0.1880	0.1692	-0.01105	0.9362
Biochemical Test				
Uric acid	0.3503	<0.01 **	0.2449	0.0716
LDH	0.3154	<0.05 *	0.09323	0.4984

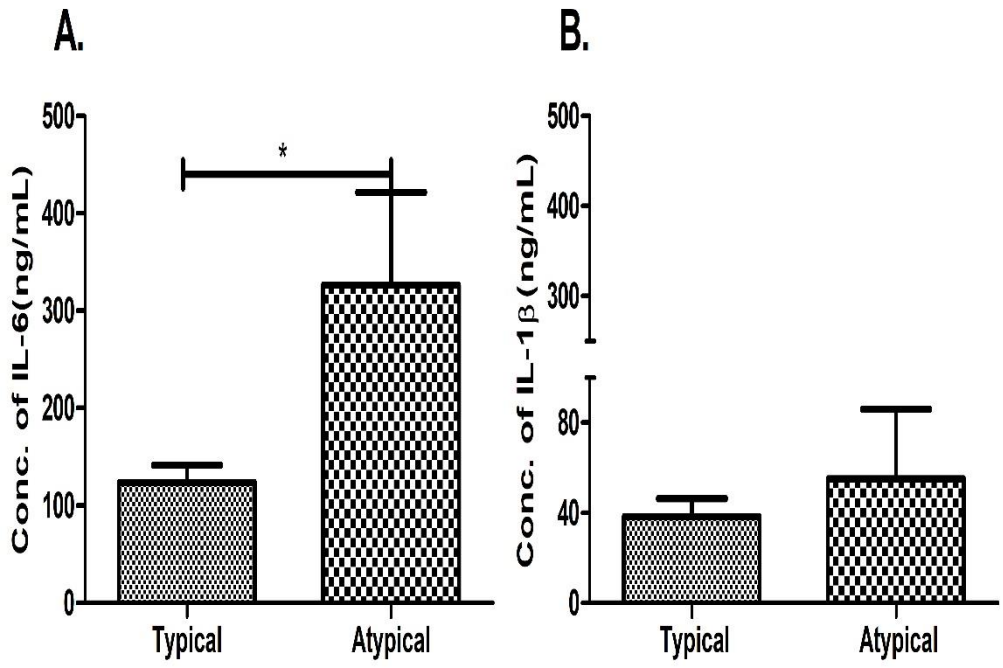

Figure 2: A. IL-6 levels in typical and atypical forms of CML; B. IL-β levels in typical and atypical forms of CML

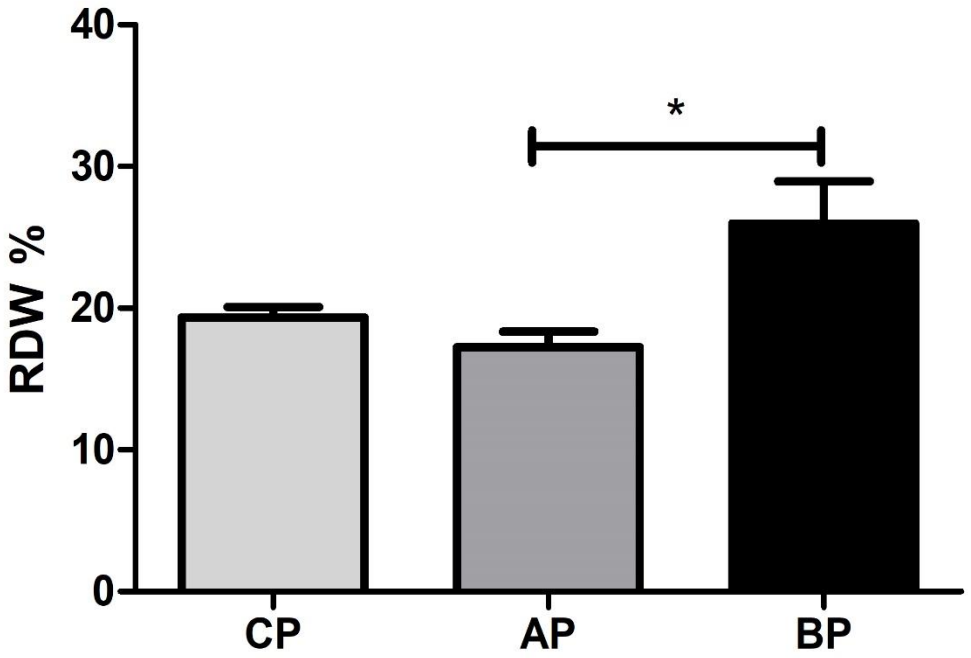

Figure 3: RDW levels in different phases of CML

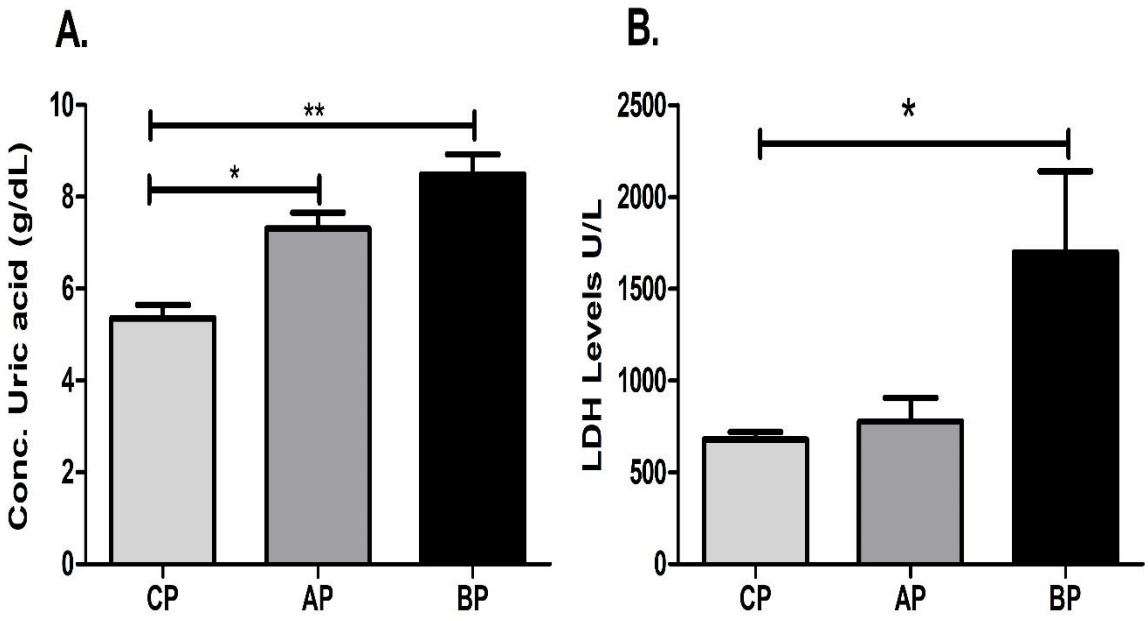

Figure 4: Biochemical parameters in different phases of CML

However a negative correlation with haemoglobin was observed although statistically insignificant which diverged from the findings observed from the current study. According to Shayamma et al.,[18]. there was significant positive correlations ($p < 0.05$) between IL-6 and LDH in multiple myeloma patients. Similarily Singh et al.,[19]. performed a study to determine the role of IL-6 in CML, and reported positive correlation between IL-6 levels and different parameters such, LDH and uric acid. These correlations were statistically significant was observed. The present research had positive correlation with spleen size, LDH and uric acid which was consistent with the existing

literature and statistical significance was detected solely between IL-6, LDH and uric acid levels. Maccio et al., [20]. observed a significant negative correlation between Hb levels and the stage of disease in epithelial ovarian cancer. Similarly, IL-1β demonstrated associations with various laboratory parameters in CML. A positive correlation was observed with total leukocyte count, platelets, lymphocytes, blasts, RBC, MCH, uric acid, and LDH levels. Conversely, a negative correlation was noted with parameters such as haemoglobin, basophils, monocytes, MCV, MCHC, RDW, spleen size, APTT, and PT. However, these correlations were statistically insignificant. Wetzler's et al.,[21]. findings suggest association between IL-1β levels and CML prognostic criteria, particularly in patients in the AP/BP phases of the disease. Elevated levels of IL-1β were significantly linked with increased blasts in the marrow, extremes in platelet counts, and peripheral blood ($p < 0.01$).The blast cells had no correlation with IL-1β .

5. Conclusion

CML progression is related with alterations in several laboratory markers, including an increase in total leukocyte count, basophils, blast cells, spleen size and pro inflammatory cytokines. These changes can provide valuable insights into the diagnosis and monitoring of CML patients at different stages of the disease. The presence of blast cells in the advanced stages may indicate that the disease is more aggressive and proliferative. The current work aims to explore the precise functions of these cytokines in the etiology of CML and assess their potential as therapeutic targets or biomarkers for disease monitoring. Regular monitoring of these parameters is crucial for managing CML patients and determining appropriate treatment strategies. Investigations of the correlations between the RDW values, interleukins may provide new insights into CML therapy.

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Conflict of interest

None

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