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Study of various biomarkers in Chronic Lymphocytic Leukemia (CLL) Patients During Chemotherapy

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ABSTRACT
Background: Chronic lymphocytic leukemia (CLL) is the most common leukemia among adults in the world and it is characterized by a heterogeneous clinical course, ranging from stable to more aggressive disease.
Methods: Total of 86 samples were included for the study. All the samples were studied for the various biomarkers (Interleukin-6, CRP, procalcitonin, LDH, Beta-2M, Ferritin, serum Amyloid and sTREM).
Results: The highest prevalence rate found in CRP and LDH is 84 (97.67%) respectively, followed by Interleukin6 is 81 (94.18%), Ferritin is 79 (91.86%), Procalcitonin is 74 (86%), serum amyloid is 71 (82.55%), sTREM is 64 (74.41%), Beta-2-M is 53 (61.62%).
Conclusions: Markedly elevated levels of IL-6, CRP, procalcitonin, LDH, Beta-2M, ferritin, serum amyloid A, and sTREM-1 were observed at the baseline stage in CLL patients, indicating significant inflammation and potential infection burden prior to chemotherapy initiation.
Keywords: CLL, biomarkers, Baseline.

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is the most common leukemia among adults in the world.[1,2] At time of diagnosis, the vast majority of patients are asymptomatic and not in need of therapy.[3,4] Over time, approximately two thirds of all patients require treatment.[5,6] CLL is currently regarded as an incurable disease.[7,8] The relationship between chronic inflammation, cardiovascular disease and cancer is well established and there are data describing activated inflammatory pathways in CLL as well as elevated levels of inflammatory markers in serum/plasma before time of CLL diagnosis.[9,10] IL-6 is a pro-inflammatory cytokine implicated in CLL pathogenesis. Elevated IL-6 levels have been associated with advanced disease stage, aggressive clinical features, and poorer prognosis in CLL patients. IL-6 plays a role in promoting tumor cell survival and resistance to chemotherapy. CRP is an acute-phase reactant protein synthesized by the liver in response to inflammation.[11] Elevated CRP levels have been observed in CLL patients with active disease and are associated with adverse clinical outcomes.

Procalcitonin is a precursor molecule for the hormone calcitonin and is released in response to bacterial infection. While less studied in CLL compared to other malignancies, elevated procalcitonin levels have been reported in CLL patients with bacterial infections. LDH is an enzyme involved in cellular metabolism, and elevated LDH levels are often indicative of tissue damage and cellular turnover. In CLL, elevated LDH levels have been associated with aggressive disease features, advanced stage, and inferior outcomes. B2M is a component of major histocompatibility complex class I molecules and is shed into the bloodstream during cellular turnover.[11] Elevated B2M levels have been correlated with advanced disease stage, aggressive clinical features, and inferior outcomes in CLL patients. Ferritin is an iron storage protein that also serves as an acute-phase reactant. Elevated ferritin levels have been reported in CLL patients with active disease and are associated with inflammation and immune dysregulation. SAA is an acute-phase protein produced in response to inflammation. While less studied in CLL, elevated SAA levels have been associated with disease activity and progression in other malignancies. sTREM-1 is a soluble form of a cell surface receptor expressed on myeloid cells, and elevated levels are indicative of inflammation and infection. While the role of sTREM-1 in CLL is not extensively studied, increased sTREM-1 levels have been associated with infectious complications in other diseases. Monitoring various biomarkers level may aid in diagnosing and managing infections in CLL patients undergoing chemotherapy.[11] The study will focus on analyzing the levels of several key markers, including interleukin-6 (IL-6), C-reactive protein (CRP), procalcitonin, lactate dehydrogenase (LDH), beta-2 microglobulin (Beta-2M), ferritin, serum amyloid A (SAA), and soluble triggering receptor expressed on myeloid cells-1 (sTREM-1).

MATERIAL & METHODS

Data were collected from confirmed diagnoses of Chronic Lymphocytic Leukemia (CLL) patients who meet the established diagnostic criteria and fulfill the inclusion criteria. The Chemiluminescent Microparticle Immuno Assay technique was used to determine the quantitative findings of CRP (C-reactive protein) test. This assay detects the levels of CRP (C-reactive protein in serum or plasma samples based on the principle of antigen-antibody binding. Assays only need to be calibrated once every thirty days, and the reagents have a lengthy shelf life of several months.

RESULTS

In our study, routine sample blood/serum/plasma was included for the study. Total of 86 samples received from the patients of our hospital and included for the study. All the samples were studied for the various biomarkers (Interleukin-6, CRP, procalcitonin, LDH, Beta-2M, Ferritin, serum Amyloid and sTREM). The highest prevalence, found in CRP and LDH is 84 (97.67%) respectively, followed by Interleukin6 is 81 (94.18%), Ferritin is 79 (91.86%), Procalcitonin is 74 (86%), serum amyloid is 71 (82.55%), sTREM is 64 (74.41%), Beta-2-M is 53 (61.62%). Out of the total 86 samples, the highest proportion was recovered from male patients (57%), while the lowest proportion was obtained from female patients (43%). Furthermore, males between the ages group of 66 to 70 years old were more infected (37%) while females between the age group of 56 to 60 and 61 to 65 years were infected at a rate of (27%) respectively.

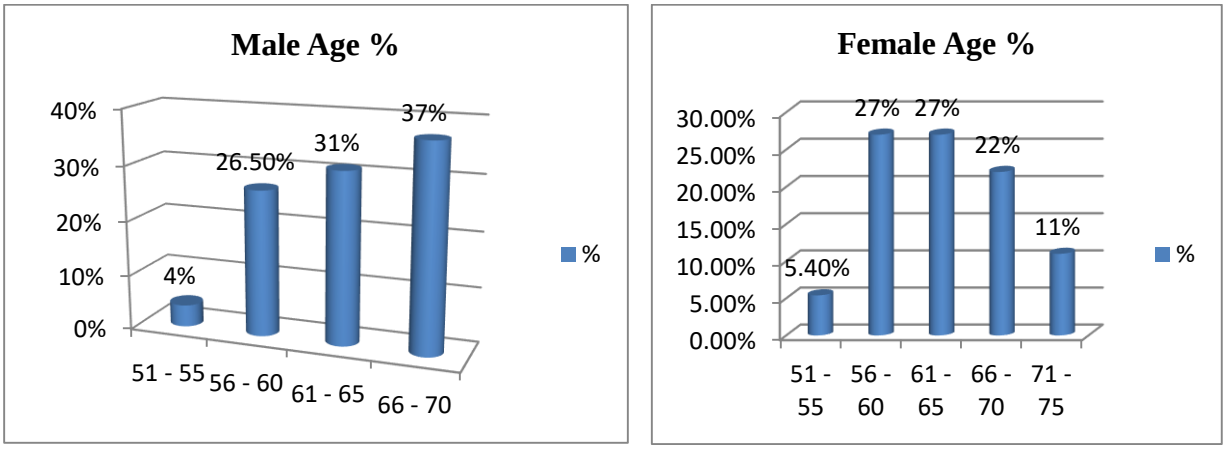

Figure 1(a): Male Age wise distribution (b) Female Age wise distribution.

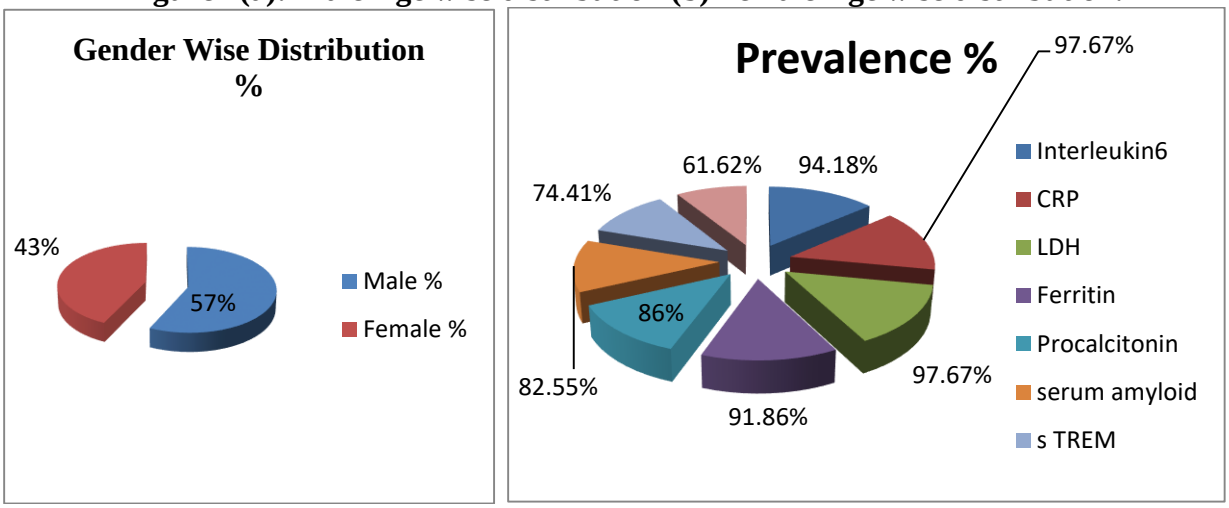

Figure 2 (a) Gender wise distribution (b)Prevalence of various biomarkers.

Baseline of various biomarkers:

S.No.	Biomarkers	Mean SD	Maximum	Minimum	p-value
1.	Interleukin-6	54.83 44.70	132.56	3.97	0.0001
2.	CRP	59.37 25.13	109.83	3.91	0.0001
3.	Procalcitonin	1.84 22.74	4.812	0.054	0.594
4.	LDH	1958.3 36.921	3979.6	195.4	0.0001
5.	Beta-2M	3.68 736.72	5.95	1.25	0.9836
6.	Ferritin	726.3 674.64	1240.7	140.2	0.0001

7.	Serum Amyloid	93.1 637.75	598.21	6.44	0.3639
8.	sTREM	882.9 596.60	1514	146.5	0.0001

DISCUSSION

All the samples were studied for the various biomarkers (Interleukin-6, CRP, procalcitonin, LDH, Beta-2M, Ferritin, serum Amyloid and sTREM). Total of 86 samples received from the patients of our hospital and included for the study. All the samples were studied for the various biomarkers (Interleukin-6, CRP, procalcitonin, LDH, Beta-2M, Ferritin, serum Amyloid and sTREM). The mean value of interleukin-6 (baseline) is 54.83 and maximum value is 132.56 and minimum is 3.97. p-value is 0.0001 and is statistically highly significant. The mean value of CRP (baseline) is 59.377 and maximum value is 109.83 and minimum is 3.91. p-value is 0.0001 and is statistically highly significant. The mean value of procalcitonin (baseline) is 1.849 and maximum value is 4.81 and minimum is 0.05. p-valus is 0.594. The mean value of LDH (baseline) is 1958.3 and maximum value is 3979.6 and minimum is 195.4. p-value is 0.0001 and is statistically highly significant. The mean value of in Beta-2M (baseline) is 3.68 and maximum value is 5.95 and minimum is 1.25. p-value is 0.9836. The mean value of Ferritin (baseline) is 76.3 and maximum value is 1240.7 and minimum is 140.2. p-valus is 0.0001 and is statistically highly significant. The mean value of serum Amyloid (baseline) is 93.01 and maximum value is 598.2 and minimum is 6.44. p-value is 03.39. The mean value of sTREM (baseline) is 882.9 and maximum value is 1514 and minimum is 146.5. p-value is 0.0001 and is statistically highly significant. The highest prevalence, found in CRP and LDH is 84 (97.67%) respectively, followed by Interleukin6 is 81 (94.18%), Ferritin is 79 (91.86%), Procalcitonin is 74 (86%), serum amyloid is 71 (82.55%), sTREM is 64 (74.41%), Beta-2-M is 53 (61.62%). The mean value of CRP (baseline) is 59.377 and maximum value is 109.83 and minimum is 3.91 and the p-value is 0.0001 and is statistically highly significant. Another study by Elizete Negreiros found that the baseline serum CRP was high in 56 (82.3 %).[12] Another study by Soojung Hong et al. that the mean value of serum CRP prior to treatment was 4.7±7.6 mg/dL; 0.3±0.2 mg/dL in the normal CRP group and 8.4±8.8 mg/dL in the high CRP group.[13] Out of the total 86 samples, the highest proportion was recovered from male patients (57%), while the lowest proportion was obtained from female patients (43%). Furthermore, males between the ages group of 66 to 70 years old were more infected (37%) while females between the age group of 56 to 60 and 61 to 65 years were infected at a rate of (27%) respectively. Another study by Pulte and Brenner, analyzed the Surveillance, Epidemiology and End Results (SEER) database based on population based cancer registries during 1973–2006 in the US, and found improvement in survival among all age groups except in the elderly population (>75 years). They also noticed a lower survival rate of 52.7% for these patients and a better survival of 72% for patients younger than 44 years.[14] Other study by Yair Herishanu et al found that the total of 107 CLL patients with CLL were reviewed. More than half of the patients were males (n = 56, 52.5%), with a mean age of 71.8 years.[15] A study by Elizete Negreiros found that the patients were predominantly male (61.8 %)

and mean age was 34 years. Fifty-three (78 %) patients had advanced stage and (76.5 %) had B symptoms. The sample was predominantly male, comprising 42 (61.8 %) men and 26 (38.2 %) women, while median age was 34 years (15 to 68 years).[12]

CONCLUSION

Markedly elevated levels of IL-6, CRP, procalcitonin, LDH, Beta-2M, ferritin, serum amyloid A, and sTREM-1 were observed at the baseline stage in CLL patients, indicating significant inflammation and potential infection burden prior to chemotherapy initiation. These findings emphasize the importance of personalized management strategies and close collaboration between clinicians and researchers to optimize CLL treatment protocols and enhance patient care. Additionally, the study underscores the significance of continuous infection risk prediction and management protocols to mitigate adverse outcomes during chemotherapy cycles.

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