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ORIGINAL ARTICLE

Clinico-Hematological profile and treatment outcome of chronic lymphocytic leukemia: A single center study from Pakistan.

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ABSTRACT… Objective: To evaluate clinical, hematological characteristics and treatment outcome of CLL patients in Pakistan. **Study Design:** Prospective Cross Sectional study. **Setting:** National Institute of Blood Diseases and Bone Marrow Transplantation (NIBD), Karachi, Pakistan. **Period:** January 2023 to November 2024. **Methods:** A total of 86 patients were included. The data was analyzed by using SPSS version 23.0. Comparative analysis was performed by using the log-rank test. The p-value of 0.05 was considered statistically significant. Overall survival was calculated by using the Kaplan-Meier method. **Results:** The study included 86 CLL patients with a median age of 59 years (IQR: 50-65 years). The male-to-female ratio was 1.86:1. Twenty-five (29.06%) patients were asymptomatic, while fatigue was the most common symptom observed in 40(46.9%) patients. Lymphadenopathy was seen in 60 (69.8%) patients with elder predominance (p = 0.038). Forty-five (52.3%) patients had anemia however, thrombocytopenia was observed in 18(20.9%) patients. Twenty-eight (32.5%) patients presented at higher-risk rai stage. A total of 61(70.9%) patients required treatment with a median interval of 4 months after diagnosis. Chlorambucil (47.4%) and ibrutinib (37.70%) were the most common regimens administered. The overall survival rate was higher in age group <55 years (74%) as compared to the elder group which was 47%. (p-value 0.072). **Conclusion:** Our study revealed that CLL in Pakistan mainly affects older adults, particularly male as seen in the western world. However, the clinical and hematological characteristics of our patients differ from existing literature. Further multicenter studies with larger sample size and prognostic biomarkers are needed to enhance risk stratification and treatment efficacy.

Key words: Chronic Lymphocytic Leukemia (CLL), Clinico-hematological Characteristics, Overall Survival, Treatment Outcome.

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is the neoplasm of small mature monoclonal B cells. According to international working group of CLL (iwCLL), clonal expansion of $\geq 5\times10^9$/L B lymphocytes expressing B cell antigens, CD19+, CD20+, CD23+ along with CD5+ in peripheral blood is necessary for the diagnosis.[1-4] The disease is characterized by lymphocytosis, infiltration of the bone marrow (BM), lymphadenopathy, and splenomegaly.[1,3,4] Morphologically, peripheral blood film in CLL usually exhibit the presence of smudge or basket cells.[1]

CLL is one of the most prevalent adult leukemia in the western world.[1,4-8] The global incidence displays notable disparities, with the western countries reporting a prevalence of over 30% of all leukemia's, whereas the far east reporting a prevalence of less than 5%.[2,9-12] However, the incidence of CLL in South Asia has tripled from 1990 to 2019, with age-standardized incidence rate (ASIR) of 0.54 per 100,000 in 2019, indicating a significant rise.[2] Some previous studies reported its incidence in Pakistan to be 9.25 to 20.1% of all leukemia.[6,13,14] Nevertheless, without a national cancer registry, it is difficult to estimate the actual incidence and therefore might be underestimated.[2] This discrepancy may be attributed to underlying genetic predisposition in the white population, as evident by the low incidence of CLL in Asian immigrants residing in North America and Europe.[2,9]

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CLL has a median age of around 70 years[1-3,5] and interestingly, it has been found to occur at relatively earlier age among the Pakistani population as compared to the western world.[1-3,9,15-17] The age of the patients is considered as a significant determinant in the long-term overall survival (OS) in the disease.

CLL is more prevalent in men compared to women with ratio ranging from 1.5 to 2:1.[3] Patients may exhibit either localized or generalized lymphadenopathy, hepatosplenomegaly, cytopenia(s), or constitutional symptoms such as fever, night sweats, or weight loss.[6] Routine blood testing is often used to make the diagnosis, as 25–50% of the patients present with no symptoms.[3] Moreover, there exists a broad range of clinical presentation; with some having a rapidly progressive disease course, while others known to have an indolent course of the disease.[4,9]

Prognosis in CLL is assessed by using binet and rai staging systems, which stratify patients into stages 0-IV or A-C.[1-3] Patients can additionally be categorized into high-risk or low-risk based on various biomarkers, including β2-microglobulin, CD38+, and ZAP70+.[3] This stratification indicates the long term prognosis and also guides the treatment outcomes.[1,3,8,9] In addition to complete blood counts (CBC), analysis of immunophenotyping, cytogenetics and molecular analysis attribute the potential to assist in the anticipation of the clinical progression, patient survival and selection of the most suitable primary therapeutic intervention.[3] Almost 80% of CLL patients have cytogenetic abnormalities, including del 13q, del 11q, del 17p, and trisomy 12.[8] Cytogenetic testing identifies subset of CLL through metaphase karyotyping, however, fluorescence in situ hybridization (FISH) is more sensitive in detecting abnormalities like del 17p.[3] Patients with del 17p have a poor prognosis due to loss of p53 function, leading to disease progression, poor treatment response, and shortened survival.[1-3,9] There are other abnormalities like unmutated IGHV, mutations in TP53, ATM, NOTCH1, SF3B1 and BIRC3 which are also associated with unfavorable outcomes, poor treatment response, and shorter survival. Therefore, they are considered as adverse prognostic factors in CLL.[1,8,18]

In the past twenty years, there has been a significant transformation in the approach to treating CLL from single-agent treatment like chlorambucil or chemo-immunotherapy (CIT) such as fludarabine in combination with cyclophosphamide (FC) or fludarabine/cyclophosphamide/rituximab (FCR) or bendamustine/rituximab (BR), to more focused and targeted therapies, including Bruton tyrosine kinase inhibitors (BTKi) and BCL-2 inhibitors such as ibrutinib and venetoclax (VEN).

A large multicenter German study reported the long-term overall survival rates of CLL patients over the period of 7.5 years and 15 years which were 72% and 33% respectively.[19] In Pakistan due to the predominance of cross-sectional studies, the evaluation of OS in CLL patients based on variations in treatment or cytogenetics has not been not conducted, resulting in a scarcity of data regarding the OS of CLL patients.[2] Among previously conducted national studies, only Mahmood et al. provided information on the two years OS, which was reported to be 65% among a cohort of 24 patients with 17p deletion. Notably, the analysis revealed no significant disparity in OS between patients with and without 17p deletion.[3] As majority of studies on CLL advancements have been carried out in developed countries and minority ethnicities have been inadequately represented in large clinical trials, the current study was aimed to assess the clinical, hematological characteristics, treatment approaches, and survival outcomes of patients diagnosed with CLL at one of the referral hematology center at a developing country, Pakistan.

METHODS

This was a cross-sectional study, conducted at National Institute of Blood Diseases and Bone Marrow Transplantation (NIBD), Karachi, Pakistan. A total of 86 CLL patients including 56males and 30 females were enrolled in this study from January 2023 to November 2024. The study was approved by Institutional review board (NIBD/IRB-280/13-2023).All participants were explained a comprehensive overview of

the research and subsequently written informed consent was taken.

Inclusion Criteria

All patients included in the study were diagnosed as CLL according to world health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissues 2016.[1]

Exclusion Criteria

Patients who were diagnosed with B-cell leukemia and lymphomas, such as Hairy cell leukemia, Follicular lymphoma, Mantle cell lymphoma and Prolymphocytic lymphoma were excluded from the study.

The diagnosis was made based on the presence of persistent lymphocytosis, evaluation of lymphocyte morphology through peripheral blood film, and analysis of immunophenotyping by flow cytometry or immunohistochemistry.

All demographic and clinical parameters were recorded. A comprehensive evaluation of the patients including a detailed history and clinical examination was done. CBC was performed by using automated analyzer Sysmex XN-1000(Sysmex Corporation, Kobe, Japan). Immunophenotyping was done by flow cytometry or immunohistochemistry to assess the panel of CLL specific markers ($CD5^{+}$,$CD10^{-}$,$CD20^{+}$,$CD23^{+}$, $CD45^{+/-}$, $CD79a^{+/-}$, $CD200^{+}$, Cyclin D1). The del17p was performed by FISH.

The Rai and Binet classification were used for staging of the disease.[1,3,8,9] Patients who did not exhibit any disease symptom(s) were followed under careful observation and the commencement of treatment was carried as per international working group of chronic lymphocytic leukemia (iwCLL) criteria.[20] The selection of treatment was determined after joint discussion by the treating physician in collaboration with the patient (shared decision making), taking into account the individual's financial situation and availability of treatment and supportive care. The interval between the diagnosis and the initiation of the first treatment was documented.[3] The response was mainly assessed as per iwCLL criteria.[20] But not all patients underwent computed tomography (CT) imaging and examination of the BM.[11] The assessment was predominantly carried out through clinical evaluation, with only minimal diagnostic tests, specifically a hemogram and an abdominal ultrasound restriction. Several patients treated for the disease showed complete resolution of clinical and laboratory manifestations; however, due to the absence of marrow restaging, they were classified as having unconfirmed complete remissions (Cru).[21] Hence treatment response was assessed as unconfirmed complete remission (CRu), partial remission (PR), progressive disease (PD), Stable disease (SD).[20]

Statistical Analysis

Descriptive analysis was calculated as mean and percentages by using statistical package for the social sciences version 23.0. The p-value of <0.05 were considered statistically significant. Survival analysis was done by using Kaplan-Meier method. OS was defined as the time from diagnosis to the date of the last follow up or death, regardless of the cause.

RESULTS

A total of 86 CLL patients were included in the study. Fifty Six (65.1%) were male and 30(34.9%) were female with an M/F of 1.86:1. The median age was 59 years (IQR 50-65 years). Twenty-six (30.23%) patients were asymptomatic and diagnosed incidentally during the routine evaluation of blood counts. Fatigue was the most common symptom at presentation, reported in 40 patients (46.5%) followed by weight loss in 32 patients (37.2%) and fever in 30 patients (34.9%). Among the clinical signs observed, lymphadenopathy was the most prevalent observed in 60 patients (69.8%), while splenomegaly was noted in 39(45.3%) patients, and hepatomegaly in 31(36.0%) patients.

The median hemoglobin (Hb) was 11(IQR 9.17-12.2 g/dL), total leukocyte count (TLC) was 52.16 (IQR 30.74-163.9 $\times$ 10□/L), absolute lymphocyte count (ALC) was 42.5$\times$ 10□ /L (IQR 22.5-154) and the median platelet count was 164(IQR 105-218$\times$ 10□/L). Anemia was found in 45(52.3%) patients, while thrombocytopenia was observed in 18(20.9%) patients. Direct Coombs Test (DCT)

was positive in 6(7%) patients.

The analysis of clinical and hematological parameters revealed significant difference after categorizing patients into two age groups with those ≤ 55 years and ≥55 years. Lymphadenopathy was significantly more prevalent among patients aged ≥55 years, with a p= 0.038 and (OR; 3.212) indicating a higher risk in this age group. Platelet count <100 was more common in the older cohort (OR; 2.091) suggesting it was twice as prevalent among elderly patients (p=0.170). Similarly, the risk of fatigue was high in >55 years of age group (OR; 1.378) with insignificant association (p= 0.476). The presence of splenomegaly was also observed more frequently in the age group≥55 years (p= 0.028).In contrast, parameters such as anemia, fever, fatigue, and weight loss did not show statistically significant difference between the two groups (p > 0.05) as shown in Table-I.

Twenty-eight (32.5%) of patients presented at advanced Rai stage (III, IV) followed by 41(47.6%) with intermediate stage (I, II) and remaining 17(19.8%) with stage (0). The distribution of patients according to Rai staging within age groups is shown in Figure-1.

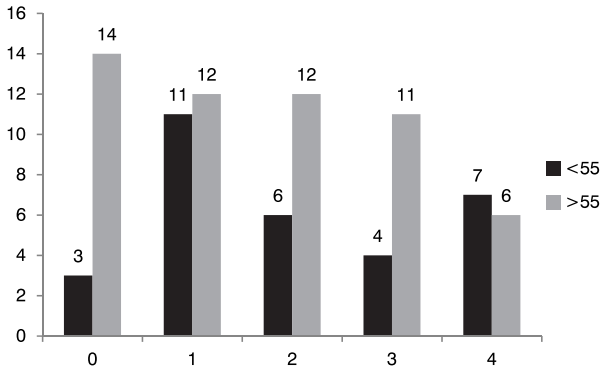

Figure-1. Rai staging with in age group.

Bone marrow examination was done in 32 patients. The pattern of infiltration was nodular in 06(7.0%) patients, interstitial in 10(11.6%), mixed in 4(4.7%) patients and diffuse in 12(14.0%) patients. In Immunophenotyping, CD38 was positive in 7 (8.1%) patients and ZAP 70 was positive in 5(5.8%) patients. The del17p was detected in 8 patients (9.3%). The β2 microglobulin levels and IGHV mutation status were not available.

Variables	Age <55 Years (n=31)	Age >55 Years (n=55)	P-Value	OR
Constitutional Symptoms:				
Unintentional Weight loss				
No	16(51.6%)	38(69.1%)	0.110	0.477
Yes	15(48.4%)	17(30.9%)		
Un-explained Fever (over two weeks)				
No	17(54.8%)	39(70.9%)	0.305	0.619
Yes	14(45.2%)	16(29.1%)		
Fatigue				
No	20(64.5%)	26(47.3%)	0.476	1.378
Yes	11(35.5%)	29(52.7%)		
Night sweats				
No	25(80.6%)	52(94.5%)	0.208	0.408
Yes	6(19.4%)	3(5.5%)		
Organ involvement:				
Hepatomegaly				
No	19(61.3%)	36(65.5%)	0.583	0.771
Yes	12(38.7%)	19(34.5%)		
Splenomegaly				
No	16(51.6%)	31(56.4%)	0.028	0.361
Yes	15(48.4%)	24(43.6%)		
Lymphadenopathy				
No	5(16.1%)	21(38.2%)	0.038	3.212
Yes	26(83.9%)	34(61.8%)		
Hematological involvement:				
Anemia (Hb<10 g/dl)				
No	15(48.4%)	30(54.5%)	0.000	0.72
Yes	16(51.6%)	25(45.5%)		
Thrombocytopenia (PLT<100× 10^9 /L)				
No	8(25.8%)	10(18.2%)	0.170	2.091
Yes	23(74.2%)	45(81.8%)		

Table-I. Clinical features of CLL patients at the time of diagnosis:

Hb:Hemoglobin, PLT: Platelets, OR: Odds ratio, n: Number of patients, %: Percentage.

Out of the 86 patients, treatment was initiated in 61(70.9%) patients, while the remaining 25(29.0%) patients had no indication of treatment and were kept on wait and watch approach. The detail of treatment administered is shown in table

02. Out of 61 patients, 16(26.22%) were switched to alternative treatments either due to primary treatment intolerance, progressive or refractory disease. These heterogeneous treatment regimens were not included for statistical analysis due to the smaller number of patients.

Treatment Administered	N (%)
First line of therapy:	
Chlorambucil	29 (47.4)
Ibrutinib	23 (37.7)
FCR	6(9.8)
VR	1(1.6)
VR+O	1(1.6)
RB	1(1.6)
Second line of therapy:	
Ibrutinib	9(14.1)
BR+I	2(3.27)
VR	2(3.27)
VR+CVP	1(1.6)
OV	1(1.6)
BR	1(1.6)

Table-II. Treatment administrated in CLL patients:

FCR: Fludarabine cyclophosphamide rituximab, VR: Venetoclax and rituximab, VR+O: Venetoclax Rituximab Obinutuzumab, RB: Rituximab Bendamustine, BR+I: Bendamustine Rituximab Ibrutinib, VR: Venetoclax Rituximab, VO: Venetoclax Rituximab Obinutuzumab

After the initial treatment regimen, a therapeutic response was observed in 61 patients. Majority of these patients had their treatment response evaluated through clinical and hematological parameters, which included constitutional symptoms, CBC parameters and the presence of organomegaly. For response assessment, the CT scan of 12(14.0%) patients, flow cytometry of 3(3.5%) and BM biopsy of 1(1.2%) patient was available. A total of 11(52.4%) patients treated with Ibrutinib and 8(47.1%) with Chlorambucil achieved PR, whereas most patients treated with Chlorambucil had SD 11(68.8%) and 3(13.04%) patients treated with Ibrutinib had SD. CRu was observed in 8(47.1%) patients treated with Chlorambucil and 7(41.2%) patients treated with Ibrutinib. Disease Progression was observed in 2(28.5%) patients on ibrutinib and 2(28.5%) on chlorambucil treatment. All 6 patients with direct antiglobulin test (DAT) positive, autoimmune hemolytic anemia (AIHA) responded to corticosteroid therapy.

Median follow-up period for age group >55 was 24 months (ranging 09-42 months) and 43 months (ranging 22-51 months) in patients <55 years of age. Sixteen (18.6%) patients were expired during the study period. The cause of death included infection(s) or disease progression. The OS rate was higher in age group <55 years with 74% as compared to the age group > 55 years which was 47%. Seven (10.93%) patients were lost to follow up (LTF) during the study period.

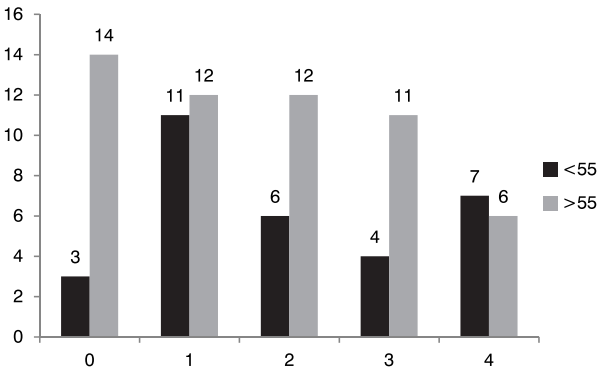

Figure-2. The overall survival of CLL patients.

DISCUSSION

CLL is the disease of small mature monoclonal B cells affecting mainly elderly population.[1,2] In the present study 63.95% CLL patients were above the age of 55 years which was also observed in a previous study.[11] The median age at the time of diagnosis was 59 years which was comparable to studies conducted in same region[6,9] indicating that CLL tends to occur at a younger age in Asian population as compared to west, where majority patients are diagnosed at 65 years of age as reported by German and African studies.[4,21] The younger age of our cohort at diagnosis could be due to variations in demographic traits, ethnicity, environmental and genetic variables, which might impact the early onset of disease in the region. However, the gender ratio was comparable to that reported in literature. In our study, CLL was found predominantly in males (65.1%) and similar sex predilection was reported by Marziye et al and Agarwal et al.[8,16] Incidental diagnosis of CLL

was reported in 30.24 % of our cases which was higher than the studies conducted by Basabaeen et al. and Ahmed et al demonstrating 7.3%. of patients being diagnosed with an incidental finding of lymphocytosis.[21,22]

In our cohort, the constitutional symptoms were prevalent. Fatigue followed by weight loss was observed in46.5% and 37.2% respectively. Notably, it was also more prevalent in the elderly group however, significant association was not observed (p= 0.476) which was similar with the findings reported by Fareed et al.[9] The studies conducted at Thailand by Agrawal et al. and India by Sriphatphiriyakun et al, observed B symptoms in 33% and 60% patients.[16,23] The presence of B symptoms could represent an advanced disease stage, suggesting systemic involvement rather than localized disease and may also indicate for the initiation of therapeutic intervention.

In our study most of the patients had lymphadenopathy (69.8%) in the elder group (p= 0.038) which was consistent with the findings of Uskudar et al and Basabaeen et al.[22,24] however, contrasting findings were reported by Agarwal et al and Sulhyan et al.[16,25] Splenomegaly was noted in (45.3%) in the elder male group (p=0.028) which was consistent with the findings of Basabeen et al. and Zeeshan et al.[6,22] In an Asian study by Agrawal et al. splenomegaly, hepatomegaly and lymphadenopathy were the first findings observed in the order of frequency.[16]

Anemia was seen in 52.3% patients which was also observed in previous studies.[23,24] Notably, Salawuet et al from Nigeria reported very high prevalence of anemia (74.4%).[26] Thrombocytopenia in our study was reported in 20.9% of the patients. In concordance to our findings, one of the previous Turkish study by Üsküdar Teke and colleagues observed thrombocytopenia in 18% of CLL patients.[24] Thrombocytopenia was common in our older group(OR; 2.091) which was similar with the results reported by Ayman et al.[27] In Rai staging, 47.6% of our patients had intermediate stage (I, II),32.5% were high-risk (III, IV), and 19.8% had stage (0) which was contrary with the findings of Basabeen et al as they observed higher risk stage in 49.1% patients.[22]

In CLL, a considerable proportion of patients may not require treatment upon presentation and can instead be monitored with wait and watch approach. Treatment is commenced when patients present with progressive lymphadenopathy, organomegaly or develop cytopenia(s) that are related to the disease. Our median time from initial diagnosis to treatment was 04 months which was similar to the results reported by Agarwal et al[16] and dissimilar with the findings of Strati et al. as they had reported a median interval of 15 months from diagnosis to the initiation of treatment.[28] This discrepancy may be explained by the fact that, as a developing nation, patients often encounter barriers to timely access to specialized diagnostic medical services and regular health screenings. Such limitations can result in identification of patients at more advanced stages.

The most common treatment regimen given in our cohort was chlorambucil (36%) which is somewhat similar with the previous reported studies.[16,23] However, chlorambucil monotherapy, has largely been abandoned by western countries, nevertheless it is still a valid treatment option in resource-poor settings as endorsed by Deepesh et al.[29] We observed an OS rate being higher in younger age group and was 0.74% (p= 0.072) which was similar with the findings by Agarwal et al.[16] However, Gogia et al. in their study showed a similar overall median survival between two age groups.[30]

Our study had some limitations, one of which is i single-center study design, potentially reducing its applicability to other healthcare institutions. Moreover, there was a lack of complete prognostic information for a significant number of patients, including biomarkers such as β2 microglobulin levels and IGHV mutation status which were not available. A significant number of patients were lost to follow-up, which might impact the analysis of long-term survival and outcome. The assessment of treatment response was further hindered by restricted diagnostic resources, which included the lack of bone marrow examination

and advanced imaging modalities as well as the diverse treatment regimens that influenced the assessment of treatment efficacy. Nevertheless, our study highlights the demographic and presentation variance demonstrating that CLL in Pakistan presents at a younger median age and advanced disease presentation. Moreover, younger age was associated with better OS outcomes. Other observed variations might be explained by geographical and ethnic differences that affect the biological and genetic aspects of the disease.

CONCLUSION

This study highlights valuable insights into the clinical and hematological characteristics, treatment approaches, and outcomes of CLL patients in Pakistan. In our part of the world, CLL primarily affects young people, and that presentation and outcomes differ significantly from those in western populations. The challenges posed by inadequate resources for diagnosis and treatment emphasize the necessity for advancements in healthcare infrastructure and accessibility. Multicenter studies with a larger sample size and longer follow-up are required to better understand the behavior of the disease in the regional context in order to improve patient care.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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3	**Quratulain Rizvi:** Data entry.
4	**Ammara Manzoor:** Study design.
5	**Laraib Majeed:** Statistical analysis, data collection.
6	**Aisha Jamal:** Writing of manuscript.
7	**Nida Anwar:** Concept of study, designed, edited, critically reviewed, final approval.