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Original Research Article

Chronic Lymphocytic Leukemia in Kashmir: A Retro-Prospective Analysis of Clinico-Pathological Features, Treatment Patterns, and Outcomes at a Tertiary Care Center

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Abstract:

Background: Chronic lymphocytic leukemia (CLL), the most prevalent adult leukemia in Western countries, is relatively uncommon in India, where it accounts for <5% of all leukemias. Studies from India suggest that patients often present at a younger age, with distinct clinical and molecular characteristics compared to Western cohorts [6–12]. Limited data exist from northern India, particularly the Kashmir region.

Objective: To evaluate the clinico-pathological characteristics, molecular profile, treatment indications, therapeutic approaches, and short-term outcomes of CLL patients at a tertiary care center in Kashmir.

Methods: This retro-prospective observational study included 100 consecutive CLL patients diagnosed between January 2023 and June 2025 at Sher-I-Kashmir Institute of Medical Sciences (SKIMS), Srinagar. Clinical, hematological, immunophenotypic, cytogenetic, and molecular parameters were analyzed. Staging was performed using Modified Rai and Binet systems. Treatment decisions followed iwCLL criteria. Outcomes assessed included overall survival (OS), progression-free survival (PFS), response rates, and complications.

Results: The mean age at diagnosis was 63.3 years (range: 40–83), with 60% aged >60 years. A male predominance was noted (M:F = 1.43:1). Forty-one percent were asymptomatic; lymphadenopathy (26%), splenomegaly (28%), and fatigue (20%) were common findings. Anemia (30%) and thrombocytopenia (22%) were frequent laboratory abnormalities. Flow cytometry confirmed classic CLL phenotype (CD5/CD19/CD23 positivity in 95%). The most common cytogenetic lesion was del(13q) (49.4%). IGHV was unmutated in 80% and TP53 mutations were rare (3%). Modified Rai stages 0–II constituted 62% of cases; Binet Stage A comprised 52%. Fifty-two percent had no treatment indication; BR chemotherapy was the most common regimen (23%). Novel agents were used in 8% of cases. At a median follow-up of 23 months, OS was 92% and PFS was 85%. Advanced stage and cytopenias correlated with worse outcomes.

Conclusion: CLL patients in Kashmir present at a younger age and predominantly in early stages. Favorable cytogenetics (del13q) and low TP53/del17p burden contribute to excellent short-term outcomes. BR remains the main therapy due to economic constraints, though limited use of targeted agents is increasing. Larger multicenter studies with longer follow-up are required to assess long-term outcomes and optimize treatment strategies.

Keywords: Chronic Lymphocytic Leukemia, Clinico-Pathological Profile, Treatment Outcomes. Kashmir Population.

Introduction

Chronic lymphocytic leukemia (CLL), also referred to as small lymphocytic lymphoma (SLL), is a clonal lymphoproliferative disorder marked by accumulation of mature but immunologically incompetent B cells in blood, bone marrow, lymph nodes, and spleen [1]. CLL and SLL are pathologically indistinguishable, differing only in the primary site of involvement. Despite substantial research, the etiology of CLL remains unclear. Familial clustering indicates genetic predisposition,

with first-degree relatives having nearly double the risk [2]. Environmental risk factors include ionizing radiation, benzene, occupational solvents, and Agent Orange exposure [3–5]; tobacco use has also been associated with increased risk [6]. The global burden of CLL is significant, with ~191,000 new cases annually and ~61,000 deaths [7]. It constitutes greater than 30% of adult leukemias in the United States [8], typically affecting individuals around 70 years of age, with a male predominance (M:F 1.3–1.7:1) [9]. However, CLL exhibits marked geographic variation, being uncommon in Asian populations, accounting for <5% of leukemias in India [10]. South Asian cohorts often demonstrate younger age at diagnosis and more aggressive disease biology [11,12].

CLL pathogenesis involves progression from monoclonal B-cell lymphocytosis (MBL) to CLL driven by antigen-driven and antigen-independent B-cell receptor (BCR) signaling, micro environmental interactions, and genetic aberrations including del(13q), del(11q), del(17p), and trisomy 12 [13–18]. Clinical presentation varies from incidental lymphocytosis to advanced disease with B symptoms, cytopenias, and autoimmune complications [15,16].

Prognosis depends on cytogenetics (del13q favorable; del11q/del17p unfavorable), TP53 status, IGHV mutation status, and protein markers CD38 and ZAP-70 [21–23]. The iwCLL guidelines advocate treatment only for symptomatic or progressive disease [24]. While chemo immunotherapy (FCR, BR) has historically been standard, targeted agents such as BTK inhibitors (ibrutinib, acalabrutinib) and venetoclax have transformed CLL management [25,26]. However, due to economic constraints, Indian centers continue to use chlorambucil and BR widely [8].

There is a paucity of data from northern India, particularly Kashmir, where demographic, genetic, and environmental factors may alter disease patterns. This study addresses this gap by extensively analyzing clinical features, pathological markers, treatment patterns, and outcomes in CLL patients at a tertiary center in Kashmir.

Aims and Objectives

Aim: To evaluate the clinico-pathological spectrum, treatment indications, therapeutic modalities, and short-term outcomes of CLL patients treated at a tertiary care center in northern India.

Objectives

Primary Objective

- To assess clinical, demographic, and laboratory characteristics, including flow cytometry, cytogenetics, and molecular profiles.

Secondary Objectives

- To determine treatment indications and therapeutic regimens administered.
- To evaluate outcomes including OS, PFS, complications, and status at follow-up.
- To correlate clinico-pathologic and molecular features with disease stage and prognosis.

Materials and Methods

Study Design: This study was conducted as a retro-prospective observational and analytical investigation. The retrospective component involved review of medical records of all eligible patients diagnosed with chronic lymphocytic leukemia (CLL) during the initial part of the study period, whereas the prospective component included systematic enrollment and follow-up of patients presenting thereafter. The design was chosen to maximize sample size, ensure uniform data capture, and assess both baseline characteristics and real-world outcomes over time.

Study Setting: The study was carried out in the Department of Clinical Hematology and Bone Marrow Transplantation (BMT), Sher-I-Kashmir Institute of Medical Sciences (SKIMS), Srinagar, Jammu & Kashmir, India, a tertiary care referral center serving the entire Kashmir valley and adjoining regions. The department functions as the primary center for diagnosis and management of hematological malignancies in the region, utilizing standardized laboratory, flow cytometric, and molecular diagnostic facilities.

Study Period: The study included all patients with a confirmed diagnosis of CLL between January 2023 and June 2025. Both retrospective and prospective recruitment ensured comprehensive inclusion of cases diagnosed within this period.

Study Population: The study population comprised all consecutive patients diagnosed with CLL based on the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) 2008 criteria [17]. Patients were included irrespective of age, sex, performance status, or treatment status at the time of presentation. Diagnosis was confirmed by persistence of peripheral blood B-lymphocytosis and corroborative flow cytometric immunophenotyping consistent with CLL.

Inclusion Criteria

Patients were eligible for inclusion if they fulfilled the following criteria:

1. Confirmed diagnosis of CLL, defined as:

- Absolute B-lymphocyte count ≥5 × 10^9/L persisting for at least three months, and
- Flow cytometric confirmation of clonality (light-chain restriction) and characteristic im-

munophenotype ($CD5^+/CD19^+/CD23^+$ with weak CD20 and surface immunoglobulin).

2. Complete baseline staging performed according to both the Modified Rai and Binet staging systems [19,20].

3. All age groups and both sexes.

4.Ability and willingness to provide informed consent for participation and use of data for research purposes.

Exclusion Criteria

Patients with the following conditions were excluded:

1. Atypical CLL or other chronic lymphoproliferative neoplasms, including:

- Mantle cell lymphoma
- Hairy cell leukemia
- Prolymphocytic leukemia
- Other B-cell or T-cell neoplasms mimicking CLL

2. Incomplete clinical records that precluded adequate evaluation of baseline features, staging, or follow-up.

3. Refusal or inability to provide informed consent.

Data Collection and Clinical Evaluation: All patients underwent detailed and systematic evaluation at presentation. Data collection was performed using structured case-record forms and included:

Demographic and baseline characteristics

- Age at diagnosis
- Sex
- Residential location
- Relevant family history of lymphoproliferative disorders

Presenting symptoms: Each patient was assessed for:

- Fever
- Fatigue
- Weight loss
- Night sweats
- Recurrent infections
- Abdominal discomfort or fullness
- Bleeding manifestations

The presence of "B symptoms" was recorded according to standard definitions.

Physical examination: A thorough systemic examination was performed, documenting:

- Lymphadenopathy (site, size, and number of nodal groups)
- Splenomegaly
- Hepatomegaly
- Pallor, icterus, or other signs of systemic involvement
- ECOG performance status

Laboratory Investigations: Baseline laboratory evaluation was performed for all patients using standardized procedures certified by SKIMS diagnostic laboratories.

Hematological Investigations

- **Complete blood count (CBC):** performed using automated hematology analyzers, with manual verification when necessary.
- **Peripheral blood smear:** assessed for morphology, presence of smudge cells, and atypical lymphocytes.
- **Bone marrow examination:** aspirate and trephine biopsy were performed where clinically indicated (e.g., unexplained cytopenias, diagnostic uncertainty). Marrow cellularity and percentage of lymphoid infiltration were recorded.

Immunophenotyping: Flow cytometric analysis was conducted using multiparametric flow cytometry platforms. The standard diagnostic panel included:

- **B-cell markers:** CD19, CD20, CD79b
- **CLL-associated markers:** CD5, CD23, CD200
- **Other markers:** FMC7, κ/λ light chain restriction

Diagnostic scoring was interpreted according to established CLL immunophenotypic criteria.

Cytogenetic and Molecular Investigations: Cytogenetic profiling was performed using fluorescence in situ hybridization (FISH) for common CLL-associated abnormalities:

- del(13q)
- trisomy 12
- del(11q)
- del(17p)

Molecular analysis included:

- IGHV mutation status (classified as mutated or unmutated using the 98% homology cut-off).
- TP53 mutation analysis, where feasible, performed through targeted sequencing.

Biochemical Investigations: Baseline metabolic and organ-function assessment included:

- Renal function tests (serum creatinine, urea)
- Liver function tests (AST, ALT, bilirubin, albumin)
- Lactate dehydrogenase (LDH)
- Uric acid

These parameters aided in risk stratification and treatment planning.

Imaging Studies: Imaging was performed based on clinical judgment:

- **Ultrasound abdomen** for organomegaly
- **Contrast-enhanced computed tomography (CECT)** of the chest and abdomen when clinically indicated, especially for evaluating internal lymphadenopathy or suspected disease progression

Staging

All patients were staged at diagnosis using:

1. Modified Rai classification (Stages 0–IV)
2. Binet classification (Stages A, B, C)

These staging systems were used for prognostication, treatment decisions, and correlation with clinical outcomes [19,20].

Treatment Protocols: Management strategies followed the International Workshop on CLL (iwCLL) guidelines [24].

Observation ("Watch-and-Wait"): Asymptomatic patients with early-stage disease (Rai 0–II/Binet A) and without treatment indications were placed on active surveillance, with periodic clinical and laboratory monitoring.

Indications for initiating therapy

Treatment was initiated in patients exhibiting any of the following:

- Symptomatic or progressive lymphadenopathy or splenomegaly
- Progressively worsening marrow failure (anemia or thrombocytopenia)
- Lymphocyte doubling time <6 months
- Autoimmune hemolytic anemia or thrombocytopenia unresponsive to corticosteroids
- Disease-related symptoms (B symptoms)

Treatment regimens

Therapy was individualized based on age, comorbidities, cytogenetic risk factors, and financial considerations. Regimens included:

- Bendamustine–rituximab (BR)
- Chlorambucil (mainly for elderly/unfit patients)
- Bruton tyrosine kinase (BTK) inhibitors:ibrutinib or acalabrutinib
- Supportive care: growth factors, transfusions, infection prophylaxis

Patients requiring second-line therapy were treated according to disease biology and drug availability.

Follow-Up and Outcome Measures: Patients were followed at regular intervals in outpatient clinics or through inpatient reviews when necessary. Monitoring included:

Clinical follow-up

Assessment for:

- Symptom progression
- Lymphadenopathy and organomegaly
- Adverse events and treatment toxicity

Hematological follow-up: CBC and biochemical tests were repeated as needed to evaluate:

- Response to therapy
- Development of cytopenias
- Treatment-related toxicity

Outcomes Measured

- **Overall Survival (OS):** Time from diagnosis to death from any cause.
- **Progression-Free Survival (PFS):** Time from diagnosis to documented disease progression or death.
- **Response rates:** Classified as complete remission (CR), partial remission (PR), stable disease (SD), or progressive disease (PD) according to iwCLL criteria.
- **Complications:** including autoimmune cytopenias, severe infections, and transformation to Richter syndrome.

Statistical Analysis: Data were entered into Microsoft Excel and analyzed using IBM SPSS Statistics version 25.0.

- Continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR) depending on distribution.
- Categorical variables were summarized as frequencies and percentages.
- Associations between categorical variables (e.g., stage vs. cytogenetics, stage vs. symptoms) were analyzed using the Chi-square test or Fisher's exact test, as appropriate.
- Kaplan–Meier survival curves were constructed to estimate OS and PFS.
- A p-value <0.05 was considered statistically significant.

Results

A total of 100 patients diagnosed with chronic lymphocytic leukemia (CLL) were evaluated during the retro-prospective study period from January 2023 to June 2025 at Sher-I-Kashmir Institute of Medical Sciences (SKIMS), Srinagar. Patients were either evaluated during inpatient admission or followed longitudinally in the outpatient clinic. The detailed observations and results are presented below.

Age Distribution: The age distribution of the study cohort is summarized in Table 1. Patients ranged in

age from 40 to 83 years, with a mean age of 63.3 years.

Table 1: Age Distribution of Patients (N = 100)

Age Group (years)	Number of Patients	Percentage (%)
40–50	15	15
51–60	26	26
61–70	34	34
71–80	24	24
>80	1	1
Total	**100**	**100**

The majority (60%) were ≥60 years, consistent with the known age association of CLL. Notably, 15% of cases were <50 years, reflecting the presence of early-onset disease in a subset of patients.

Sex Distribution

Table 2: Gender Distribution of Patients (N = 100)

Gender	Number of Patients	Percentage (%)
Male	59	59
Female	41	41
Total	**100**	**100**

Males were more frequently affected than females (male-to-female ratio 1.43:1), in line with established epidemiological trends.

Residence: Patients originated from multiple districts across Jammu and Kashmir, including Srinagar, Baramulla, Bandipora, Pulwama, and Anantnag. No significant geographic clustering was identified. Higher representation from urban districts such as Srinagar may reflect differential health-seeking behavior or referral bias.

Clinical Symptoms

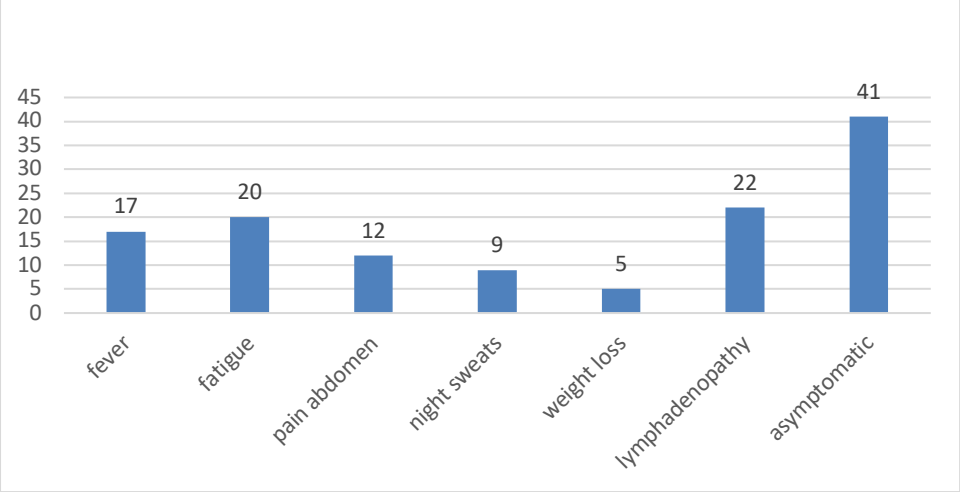

Figure 1: Clinical presentations are illustrated

A substantial proportion (41%) were asymptomatic, with incidental lymphocytosis leading to diagnosis.

Common symptoms included:

- **Lymphadenopathy:** 22%
- **Fatigue:** 20%
- **Fever:** 17%
- **Abdominal pain:** 12%
- **Night sweats:** 9%
- **Weight loss:** 5%

The predominance of asymptomatic presentation suggests early detection in many cases.

Physical Examination Findings

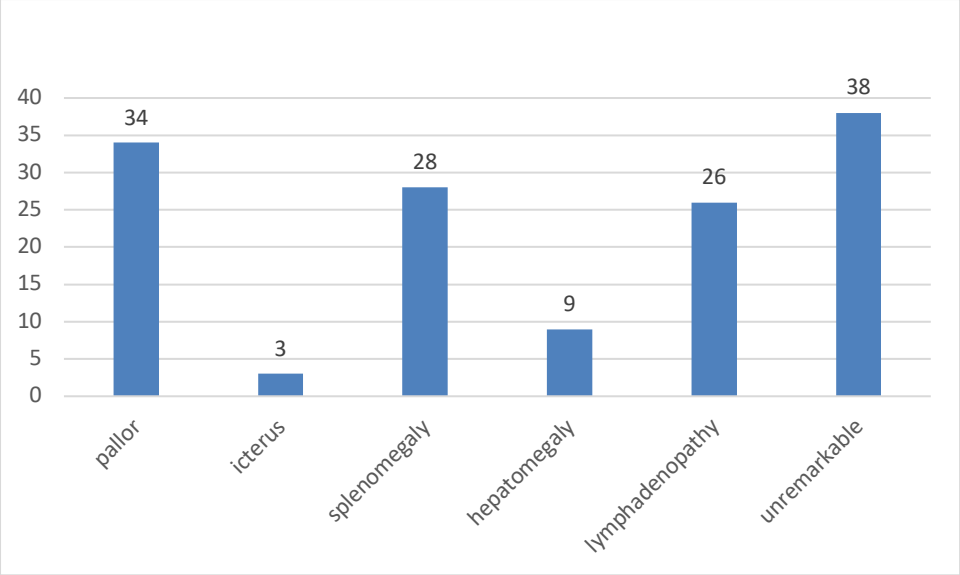

Figure 2: Physical examination revealed

- **Unremarkable findings:** 38%
- **Pallor:** 34%
- **Splenomegaly:** 28%
- **Lymphadenopathy:** 26%
- **Hepatomegaly:** 9%
- **Icterus:** 3%

These findings are consistent with marrow infiltration, cytopenias, and lymphoproliferation characteristic of CLL.

Laboratory Investigations

Complete Blood Count (CBC)

1. Hemoglobin:

- Mean: 12.0 g/dL (range 4.9–18.7 g/dL)
- Anemia (<11 g/dL): 30% of patients

2. Total Leukocyte Count (TLC):

- Mean: 64.7 ×10³/µL (range 10.8–314 ×10³/µL)
- Marked lymphocytosis (>20 ×10³/µL): 86%

3. Differential Count:

- Mean lymphocyte percentage: 78.6%

4. Platelet Count:

- Mean: 134.6 ×10³/µL
- Thrombocytopenia (<100 ×10³/µL): 22%

Peripheral Blood Film (PBF)

Diagnostic features included:

- Lymphocytosis: 100%
- Smudge cells: 60%
- Atypical lymphocytes: 33%
- Mature lymphocytes: 20%

Kidney Function Tests

- Urea: Mean 36.6 mg/dL
- Creatinine: Mean 1.1 mg/dL (significant elevation in 4 patients)

Liver Function Tests

- Total bilirubin: Mean 1.1 mg/dL
- ALT: Mean 81.5 U/L
- Hypoalbuminemia: 15%

Other Laboratory Markers

- **LDH:** Elevated in 30% (mean 241.6 U/L)
- **Uric acid:** Elevated in 10%
- **Viral serology:** Hepatitis B positive in 2 patients
- **Coagulation profile:** Normal

Imaging (Ultrasound Abdomen/Pelvis, n=86)

Findings included:

- **Splenomegaly:** 18 patients (13.8–22 cm)
- **Hepatomegaly:** 1 patient
- **Abdominal lymphadenopathy:** 8 patients (nodes up to 4 cm)
- **Hepatosplenomegaly with LAP:** 17 patients
- **Normal study:** 42 patients

Ultrasound findings correlated with disease burden and clinical staging.

Bone Marrow Aspiration and Biopsy: Bone marrow evaluation showed:

- Hypercellular marrow with mature lymphoid infiltration (mean 80%)
- Infiltration ranged from 43% to 97%
- Marrow biopsy confirmed CLL morphology and replacement of hematopoietic tissue

Immunophenotyping

Flow cytometry demonstrated classical CLL immunophenotype:

- CD45: 100%

- CD5: 95%
- CD19: 95%
- CD20: 95%
- CD23: 95%
- CD200: 90%
- Additional markers: CD38, CD43, CD79b, ROR1 in subsets

Co-expression of CD5/CD19/CD23 confirmed the diagnosis in all cases.

Genetic and Molecular Markers

IGHV Mutation Status (n=86)

- **Mutated:** 17 (20%)
- **Unmutated:** 69 (80%)

TP53 Mutation (n=84)

- Wild Type(WT): 80 (95%)
- Mutated: 4 (5%)

ZAP70 (n=25)

- Positive: 4 (16%)

Cytogenetics

- **13q deletion:** 49.4%
- **Trisomy 12:** 16.2%
- **11q deletion:** 7%
- **17p deletion (high-risk):** 3.4%

Immunoglobulin Levels (n=15)

- Mild to moderate hypogammaglobulinemia noted in several patients

These findings indicate a predominance of favorable-risk cytogenetic abnormalities.

Staging

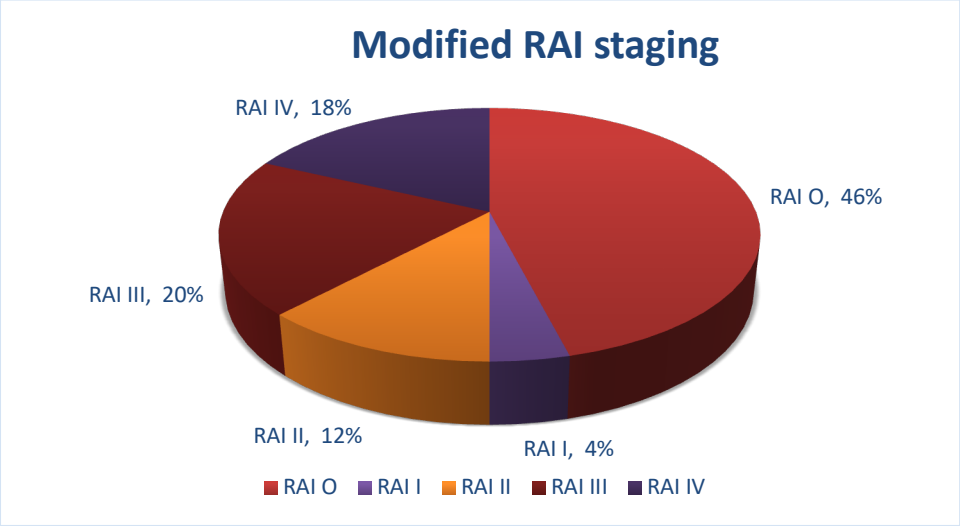

Figure 3:Modified Rai Staging

- Stage 0: 46%
- Stage I: 4%
- Stage II: 12%
- Stage III: 20%
- Stage IV: 18%

Early-stage disease (Stage 0–II) accounted for 62%, while 38% had advanced-stage disease.

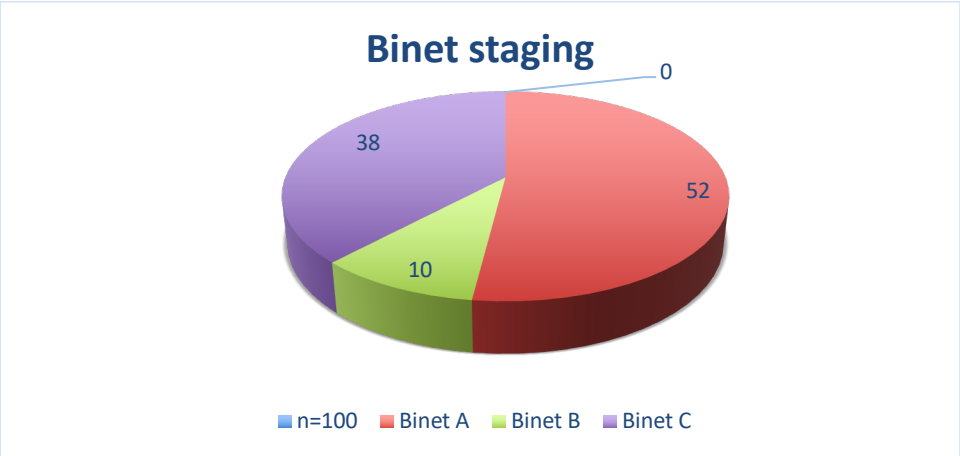

Figure 4: Binet staging

Binet Staging

- Stage A: 52%
- Stage B: 10%
- Stage C: 38%

CLL-IPI Score (n=10)

- Low risk: 70%
- Intermediate risk: 30%
- High risk: 0%
- Not available for 90% of patients

Treatment Indications and Outcomes

Treatment Indications

- No indication for therapy: 63%
- Anemia: 16%
- Thrombocytopenia: 10%
- Rapid lymphocyte doubling (<6 months): 4%
- Anemia + thrombocytopenia: 7%
- Anemia + high-risk cytogenetics: 2%
- B symptoms: 1%

Treatment Received

- No therapy (watch-and-wait): 63%
- BR regimen: 23%
- Acalabrutinib: 5%
- Ibrutinib: 3%
- Second-line therapies: 6%

Second-line regimens included BR/Acalabrutinib (3 patients), BR/Venetoclax (1 patient), Rituximab/Acalabrutinib (1 patient), and Wysolone/Acalabrutinib (1 patient).

Follow-Up

- Median follow-up: 23 months
- Mean follow-up: 26 months

Survival Status

- Alive: 92%
- Dead: 8%

Most deaths occurred in advanced-stage patients or those with adverse genetic markers.

Discussion

Chronic lymphocytic leukemia (CLL) is a biologically heterogeneous disorder with diverse clinical presentations, molecular profiles, and outcomes across populations. Although it is the most common leukemia in Western countries, its incidence in Asian regions, including India, remains substantially lower, accounting for only 1.7–8.8% of all leukemias compared to 2530% in the West [1]. This retro-prospective study conducted at Sher-I-Kashmir Institute of Medical Sciences (SKIMS), Srinagar, from January 2023 to June 2025, provides valuable insights into the clinico-pathological spectrum of CLL in the Kashmir valley, a region with unique demographic, environmental, and healthcare characteristics. Our findings demonstrate a blend of patterns consistent with both Indian and international cohorts, while also revealing region-specific distinctions, particularly in age at presentation, cytogenetic distribution, and treatment pathways. These observations are essential for improving local diagnostic strategies, prognostication, and therapeutic planning.

Demographic Profile: The median age of 63.3 years in our study population is younger than that seen in Western cohorts, where the median age at diagnosis is approximately 70 years [1,7]. This trend, however, aligns with several Indian studies reporting median ages of 60–61 years. Agrawal et al. reported a median age of 61 years [6], Mukkamalla et al. noted 60 years [7], and Tejaswi et al. documented 61 years [8], confirming that CLL in India tends to occur roughly a decade earlier than in Western populations. Although CLL is typically considered a disease of the elderly, 15% of our patients were aged ≤50 years. This figure, while lower than the 28% reported in Sudanese studies [10], remains higher than Western registries, where younger patients constitute <10% [1]. This may reflect regional genetic factors or increased incidental detection in younger individuals undergoing routine blood tests.

A pronounced male predominance was observed (M:F = 1.43:1), consistent with Indian and global literature [6–8,18]. The persistent male preponderance raises the possibility of underlying genetic predispositions, occupational exposures, or health-seeking behaviors influencing gender distribution.

Clinical Presentation

A notable finding of the present study is that 41% of patients were asymptomatic at diagnosis. This proportion mirrors Western series where over 40% of cases are detected incidentally through routine health checks [1], but is much higher than older Indian reports where incidental detection was rare (Agrawal et al.) [6]. This shift likely reflects increased availability of complete blood counts, better healthcare outreach, and improved physician awareness.

Among symptomatic patients, lymphadenopathy (26%) and splenomegaly (28%) were common findings, aligning with the results of Mukkamalla et al [7]and reflecting underlying lymphoproliferation. Pallor was detected in a relatively high proportion (34%), indicating anemia due to marrow infiltration, chronic disease, or autoimmune mechanisms.

Constitutional “B symptoms,” present in 17% of patients, fell within the global reported range of 15–25% [5]. Autoimmune cytopenias were noted in 7% of our cohort, somewhat lower than the 10–

20% cited in Western literature [16]. Overall, our results suggest a transition toward earlier disease detection in the region, similar to international trends.

Laboratory Findings: Classical laboratory features of CLL were observed. Lymphocytosis was prominent, with a mean ALC of 64.7 × 10⁹/L. Smudge cells—a hallmark of CLL—were present in 60% of cases, consistent with established hematologic descriptions [17]. Anemia (30%) and thrombocytopenia (22%) were relatively common.

These findings reflect advanced disease in a subset of patients and correlate closely with Rai III–IV staging, which encompasses cytopenias due to marrow failure or hypersplenism. Elevations in LDH and hypoalbuminemia were also seen in some patients, indicating high tumor burden or systemic inflammatory effects.

Cytogenetic and Molecular Profile: Cytogenetic evaluation remains a cornerstone of modern CLL assessment. In our study, del(13q) was the most frequent abnormality (49%), aligning with findings from multiple Indian and Western reports [6,11,13]. This aberration is generally associated with favorable prognosis.

Trisomy 12 (16%) and del(11q) (7%) were observed at rates comparable to global averages [13].The prevalence of del(17p) (3.4%) and TP53 mutations (5%) was lower than typically reported in Western populations, where these abnormalities occur in 7–10% of cases at diagnosis [13,15]. This is clinically significant because del(17p)/TP53 mutations are strong predictors of poor response to standard chemotherapy and inferior survival.

Interestingly, IGHV mutation status was unmutated in 80% of assessed patients, reflecting a predominance of biologically aggressive disease. While this finding mirrors some Indian data [8], it differs from Western studies where mutated and unmutated IGHV tend to be more evenly distributed [12]. This discordance presents a prognostic paradox in our cohort: while unmutated IGHV is generally an adverse marker, the high prevalence of del(13q) and low frequency of TP53/del(17p) abnormalities suggest an overall favorable disease course.

Immunophenotyping in all patients confirmed classical CLL markers—CD5, CD19, CD20, CD23, and CD200—consistent with WHO diagnostic criteria. Expression of CD38 and ZAP-70 in subsets of patients supports existing evidence linking these markers with more aggressive disease biology.

Staging at Presentation: Modified Rai staging revealed that 62% of patients presented with early-stage disease (0–II), while 38% had advanced-stage disease. Similarly, according to Binet classification, 52% were Stage A, 10% Stage B, and 38% Stage C. These findings are consistent with recent Indian reports, such as that of Tejaswi et al. [8], where a majority of cases were diagnosed at an early stage.

This contrasts sharply with older Indian studies (e.g., Agrawal et al. [6]), where most patients presented with symptomatic or advanced disease. The shift suggests increasing early diagnosis likely due to routine hematology testing, improved medical surveillance, and greater diagnostic awareness.

Treatment Patterns: Management strategies followed the iwCLL guidelines [24]. Observation ("watch-and-wait") was the approach for 61.5% of patients who lacked treatment indications. This proportion is consistent with global recommendations and reflects the indolent nature of CLL in many individuals.

Among patients requiring treatment, bendamustine-rituximab (BR) was the most frequently used regimen (23%), mirroring patterns reported in Indian cohorts [8]. Novel targeted therapies such as ibrutinib and acalabrutinib were used in 7% of patients.

In contrast, frontline therapy in many Western settings now frequently incorporates BTK inhibitors and venetoclax-based regimens [25]. Financial and resource constraints in India significantly influence treatment choices, explaining continued reliance on BR and chlorambucil.

The predominant triggers for treatment initiation in our study—anemia and thrombocytopenia—are indicators of marrow failure and align with iwCLL criteria and international experience.

Treatment Outcomes: The overall response rate (ORR) for patients treated with the BR regimen was approximately 80%, higher than chlorambucil (40%), and consistent with results from Tejaswi et al. [8] and global data demonstrating superior efficacy of chemo immunotherapy over alkylating agents.

Targeted therapies (ibrutinib, acalabrutinib) showed excellent disease control in the patients who received them, aligning with international evidence demonstrating their efficacy in both frontline and relapsed disease settings [25].

Treatment-related adverse effects were within expected ranges, with neutropenia (24%) and infections (16%) comparable to global registries and clinical trials.

Survival Outcomes: After a median follow-up of 23 months, overall survival (OS) in our cohort was 92%, with progression-free survival (PFS) at 85%. These outcomes are superior to earlier Indian

reports where median OS ranged from 4 to 6 years [6,7].

The favorable outcomes in our study may be attributed to:

1. High proportion of early-stage disease at diagnosis
2. Predominant presence of favorable cytogenetics (del(13q))
3. Low incidence of TP53 abnormalities
4. Use of BR and targeted agents in appropriate patients

These observations align with the CLL-IPI model [15], reinforcing the prognostic significance of age, stage, β2-microglobulin levels, IGHV status, and TP53 abnormalities.

Clinical Implications: The findings highlight the value of simple diagnostic tools—such as lymphocyte counts, peripheral smear evaluation, and flow cytometry with CD5/CD19/CD23 markers—as reliable cornerstones for confirming CLL.

Routine assessment of key prognostic indicators, including 13q deletion and IGHV mutation status, remains essential for accurate risk stratification and individualized management. While most early-stage patients can be safely managed with a watch-and-wait approach, those presenting with cytopenias, symptomatic disease, or rapid progression may benefit from targeted therapies such as BTK inhibitors. This study also lays the groundwork for future research exploring regional variations, prognostic molecular markers, and real-world effectiveness of novel therapies in the Kashmiri population.

Limitations

This study is limited by incomplete data for certain prognostic parameters, including CLL-IPI scores, immunoglobulin profiles, and some cytogenetic results, which restricts deeper risk-based analyses. The relatively short follow-up period prevents robust assessment of long-term outcomes such as durable response, progression-free survival, and late complications.

Additionally, as the study reflects patient data from a single region in Jammu and Kashmir, the findings may not be fully generalizable to broader populations. Although the sample size of 100 patients provides meaningful insights, larger multicenter studies are needed to enhance statistical strength and external validity.

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