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– ORIGINAL PAPER –

A Retrospective Analysis of CLL Patients in a Romanian Hematology Center

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Abstract

Background: *Chronic lymphocytic leukemia (CLL) is the most common form of leukemia in adults and is characterized by a heterogeneous clinical course. Understanding real-world management and prognostic factors is essential for optimizing outcomes.*

Methods: *We conducted a retrospective study of 112 CLL patients treated at Colentina Clinical Hospital, Bucharest, from January 2009 to June 2025. Clinical and biological data—including Binet stage, Charlson Comorbidity Index (CCI), cytogenetic and molecular markers—were collected and analyzed. Time to first treatment (TTFT), treatment patterns, and response rates were evaluated. Statistical tests included Mann-Whitney U and Fisher's exact test, with $p < 0.05$ considered significant.*

Results: *The cohort had a median age of 65 years, with a male predominance (58%). Binet stages A, B, and C were distributed as 43.8%, 42.0%, and 14.3%, respectively. Half of the patients remained in watch and wait, while 50% initiated treatment after a median TTFT of 2.2 months. The most used first-line regimens were Obinutuzumab-Venetoclax (25.5%), Acalabrutinib (21.8%), and Ibrutinib-Venetoclax (14.5%). Complete response was achieved in 70.9% of treated patients. Treatment initiation correlated significantly with Binet stage ($p < 0.001$), and trends were observed with unmutated IGHV (91.3% treated), and high-risk cytogenetics (75.0% treated). A CCI score >4 was associated with a 21.12% increased risk of death ($p = 0.005$).*

Conclusions: *In this real-world cohort, Binet stage remained a strong predictor of treatment initiation, while comorbidities and molecular markers showed variable influence. These findings highlight the value of integrating clinical staging with molecular profiling to guide therapeutic decisions in CLL.*

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Introduction

Chronic lymphocytic leukemia (CLL) / small lymphocytic lymphoma (SLL) is a chronic lymphoproliferative disorder [1] caused by defective apoptosis that leads to excessive accumulation of B lymphocytes—initially in the bone marrow and peripheral blood, and progressively in lymph nodes, spleen or other tissues [1]. The abnormal B lymphocytes appear morphologically mature but are functionally and immunologically incompetent [2]. CLL typically follows a relatively slow clinical course, but disease progression over time leads to the need for individualized treatment according to international consensus criteria for active disease.

CLL is most commonly diagnosed in individuals aged 50–70, with a median age at diagnosis of 72 years. It is extremely rare under the age of 30, with an increasing incidence after the age of 70 and exponential growth after 80. In Europe, the incidence is approximately 4.2 per 100,000/year, rising to over 30 per 100,000/year in individuals over 80 years old [2].

CLL and SLL are different clinical manifestations of the same disease and are managed similarly. As the disease progresses, abnormal hematopoiesis leads to cytopenias, along with reduced immunoglobulin production, which increases the risk of infections due to immune dysfunction [3]. CLL is also associated with autoimmune cytopenias and a 2–7-fold increased risk of secondary malignancies [3].

Constitutive activation of BCR signaling pathways plays an important pathogenic role in CLL [4]. Research targeting various kinases involved in the BCR pathway has led to significant advances in therapy for this disease. From a genetic standpoint, abnormal karyotypes are found in the majority of CLL patients, with structural abnormalities identified in more than 80% of cases [5]. The most common abnormalities include deletion 13q (present in over 50% of patients), trisomy 12 (in 10–20%), deletion 11q, and deletion 17p [1].

Molecular biomarkers like cytogenetic analysis, mutational status of immunoglobulin heavy chain variable gene locus (IGHV) and TP53 provide insight into the underlying pathogenesis of the disease and are also used as predictors of time to progression, time to need for therapy and overall survival. [4].

Materials and Methods

We retrospectively reviewed the records of CLL patients from the Hematology II Department of Colentina Clinical Hospital. Clinical data collected from day-to-day documentation charts included age and date of CLL diagnosis, Binet staging, sex, comorbidities using Charlson Comorbidity Index (CCI), and laboratory parameters. Genetic abnormalities analyzed were del(17p), del(11q), del(13q), TP53 mutation, and IGHV status, first and second line treatment regimens as well as progression and survival status.

We have performed descriptive statistics for demographics, Binet stage and mutational status. Outcomes of interest included time to first treatment (TTFT), follow-up duration, number of therapy lines, and vital status. TTFT was computed as the time between diagnosis and treatment initiation. Follow-up was censored at the time of analysis. Additionally, we have analyzed the treatment effectiveness including duration of therapy and evaluating the response according to International Workshop on CLL criteria.

Statistical analyses were conducted using IBM SPSS Statistics version 25 (IBM Corp., Armonk, NY, USA), Epi Info version 7.2 (Centers for Disease Control and Prevention, Atlanta, GA, USA), and Microsoft Excel from the Microsoft 365 suite (Microsoft Corp., Redmond, WA, USA). Categorical variables were summarized as absolute frequencies and percentages. The Mann-Whitney U test was employed to compare differences between independent groups. For analyses involving small sample sizes, the mid-p method and Fisher's exact test were applied. Associations between dichotomous variables and outcomes were assessed using odds ratios. A two-tailed p-value of less than 0.05 was considered statistically significant throughout the study.

Results

We have identified 112 patients in our hospital database who were diagnosed with CLL between January 2009 and June 2025. Median age at diagnosis was 65 years and slightly more males (58%) vs. females.

Patient Characteristics

Demographic and comorbidity summaries are presented in Tables 1–3.

Characteristic	N (%)
Sex (M/F) - M	65 (58.0%)
Sex (M/F) - F	47 (42.0%)
(CCI ≤4)	71 (63.3%)
(CCI >4)	41 (36.6%)
IGHV Status – missing	72 (64.3%)
IGHV Status - No	23 (20.5%)
IGHV Status - Yes	17 (15.2%)

del(17p) - missing	62 (55.4%)
del(17p) - No	45 (40.2%)
del(17p) - Yes	5 (4.5%)
del(11q) - missing	91 (81.2%)
del(11q) - No	16 (14.3%)
del(11q) - Yes	5 (4.5%)
TP53 Mutation - missing	61 (54.5%)
TP53 Mutation - No	43 (38.4%)
TP53 Mutation - Yes	8 (7.1%)

Table 1. *Demographic Summary*

Comorbidity	N (%)
Hepatites	**13 (11.6%)**
Diabetes	**16 (14.3%)**
Lung disease	**9 (8.0%)**
Solid tumor	**9 (8.0%)**
Psychiatric disease	**6 (5.4%)**
Infections	**20 (17.9%)**
Endocrine pathology	**4 (3.6%)**

Table 2. *Demographic Summary*

Binet Stage	**N %**
A	49 (43.8%)
B	47 (42.0%)
C	16 (14.3%)

Table 3. *Demographic Summary*

First-line Treatment Patterns

Regarding the therapeutic approach, 56 patient (50%) remained in watch and wait, while for the other 50% first-line treatment was initiated after a median follow-up time of 2.2 months (mean TTFT was 9.8 months).

The most used first-line regimens were Obinutuzumab-Venetoclax (25.5%), Acalabrutinib (21.8%), and Ibrutinib-Venetoclax (14.5%). Less frequent regimens included Chrolambucyl (9%), RFC (7.3%) and Rituximab-Chlorambucyl (7.3%)). The full distribution is shown in Table 4.

First-line Regimen	**N (%)**
Obinotuzumab + Venetoclax	14 (25.5%)
Acalabrutinib	12 (21.8%)
Ibrutinib + Venetoclax	8 (14.5%)
RFC	4 (7.3%)
R Chlorambucyl	4 (7.3%)
CVP	3 (5.5%)
Chlorambucyl	5 (9%)
Rituximab	1 (1.8%)
Ibrutinib	3 (5.5%)
R CHOP	1 (1.8%)

Table 4*. Distribution of First-line Treatment Regimens*

Response to First-line Treatment

Most patients (70.9%) achieved a complete response, while 8 patients (14.5%) progressed after first line treatment during the follow-up period.

Treatment Initiation by Clinical and Biological Characteristics

Treatment patterns varied significantly across Binet stages. Among patients with Binet stage A, 5 out of 49 patients (10.2%) initiated treatment. In contrast, 76.6% of those with stage B and 93.8% with stage C received therapy. Median TTFT varied significantly between Binet stages, 38.4 months, 9.8 months and 2.2 months for Bine stages A, B and C, respectively.

For IGHV mutation status, 91.3% of patients with unmutated IGHV received treatment, compared to 70.6% with mutated IGHV in the tested population.

Regarding high-risk cytogenetics (defined as del17p and/or TP53 mutation), 75.0% of patients with high-risk features initiated treatment, compared to 47.1% of those without.

Analysis by comorbidity stage (CCI score) showed similar treatment proportions: 46.3% of patients with low comorbidity (CCI ≤ 4) received treatment, compared to 50.7% of those with high comorbidity (CCI > 4). However, a Charlson Comorbidity Index (CCI) score greater than 4 was associated with a 21.12% increased risk of death (p = 0.005).

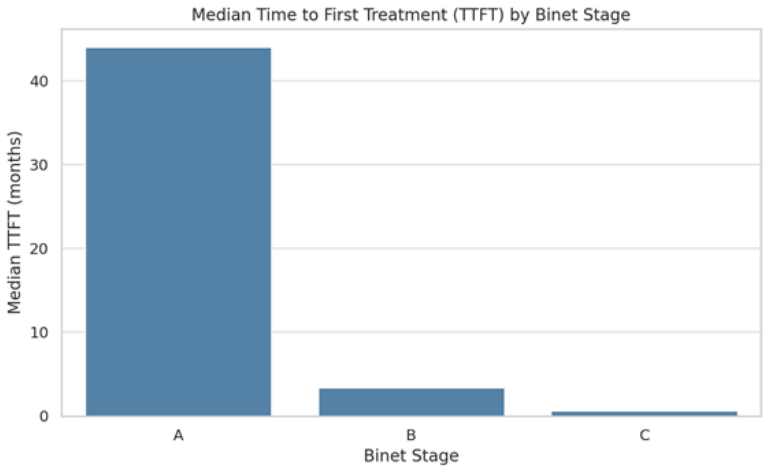
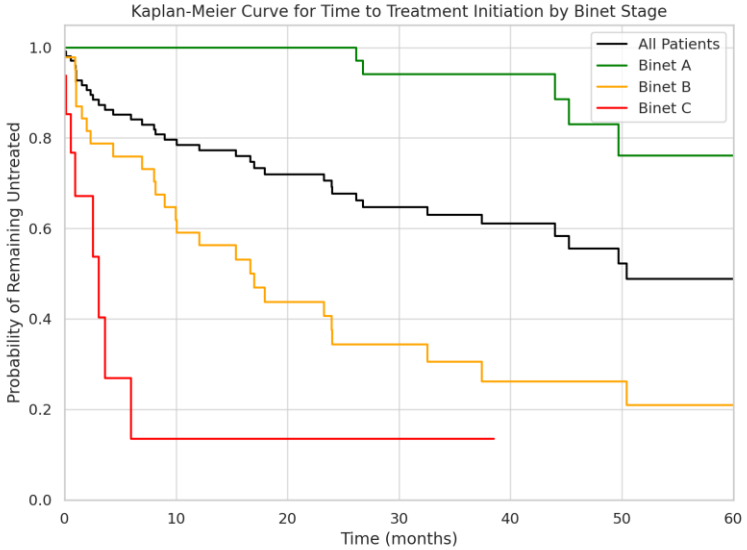


Figure 1. *Median Time to First Treatment and Kaplan-Meier curve for TTFT by Binet Stage*



Second-line Treatment Patterns

A total of 12 patients (21.8% of those treated) received valid second-line therapy. The most common second-line regimens included Rituximab + Venetoclax (5 (41.7%), Ibrutinib (2 (16.7%)), and Acalabrutinib (2 (16.7%)). Full details are shown in Table 5.

The reasons for discontinuation of first-line treatment were as follows: relapse in 5 patients, progression in 4 patients, and intolerance in 1 patient.

Second-line Regimen	N	%
Rituximab+VENetoclax	5	5 (41.7%)
Ibrutinib	2	2 (16.7%)
Acalabrutinib	2	2 (16.7%)
Chlorambucyl	2	2 (16.7%)
EPOCH	1	1 (8.3%)

***Table 5**. Second-line regimens*

Among the 56 patients who received first-line treatment, responses were documented in 52 cases. The most frequent response was RC (39 (70.9%), followed by PD (7 (12.7%)).

Discussion

In this retrospective analysis of 112 patients with chronic lymphocytic leukemia (CLL), we observed that exactly half were managed with a watch and wait (W&W) strategy. This proportion is consistent with established clinical practice, where immediate treatment is deferred in early-stage, asymptomatic CLL, as recommended by the IWCLL guidelines [5]. Several population-based studies have reported W&W rates ranging from 30% to 50% depending on the cohort characteristics and referral bias [6,7]. Our data reaffirm the importance of active surveillance in early CLL and highlight the need for clinical and biological markers to stratify the risk of progression.

Among those who received treatment, Binet staging at diagnosis demonstrated a statistically significant correlation with treatment initiation, with 93.8% of stage C and 76.8% of stage B patients undergoing therapy, compared to only 10.2% in stage A. This is in line with classical prognostic models that emphasize the relevance of clinical staging in guiding therapeutic decisions [8,9]. Our findings are compatible with historical data validating Binet and Rai staging systems as primary indicators of disease burden and progression.

Although not statistically significant in our cohort, patients with unmutated IGHV status were more likely to be treated (91.3%) compared to those with mutated IGHV (70.6%). Unmutated IGHV has been consistently associated with more aggressive disease biology and shorter TTFT in several large studies such as CLL8 and CLL10 [9,10]. The absence of statistical significance in our series may reflect sample size limitations or overlapping risk features that affect treatment decisions.

Similarly, patients with high-risk cytogenetic features—defined by del(17p) and/or TP53 mutations—were more frequently treated (75.0%) compared to patients without these alterations (47.1%), though this difference did not reach statistical significance. This trend is consistent with international data showing early progression and poor response to chemoimmunotherapy in this subgroup [11,12]. Newer therapies, including BTK inhibitors and BCL2 antagonists, are increasingly being used upfront for these patients, a trend also visible in our dataset.

The presence of comorbidities, as measured by the Charlson Comorbidity Index (CCI), did not significantly influence treatment decisions in our study. This finding contrasts with other reports where higher CCI scores were associated with less aggressive treatment choices or delays in therapy initiation [13]. It is possible that clinical judgment, availability of less toxic targeted therapies, or institutional practice patterns may modulate this relationship in real-world settings.

This study reinforces the value of Binet staging as a practical and prognostically relevant tool for guiding treatment initiation. While trends regarding IGHV status and high-risk cytogenetics align with broader literature, the lack of statistical significance highlights the need for larger cohorts or pooled analyses. Our retrospective design, reliance on electronic medical records, and limited molecular data for all patients are important limitations. Nevertheless, this analysis contributes valuable insight

into the real-world management of CLL in an academic hematology center.

Conclusions

This retrospective cohort study provides real-world insights into the clinical and biological characteristics, treatment patterns, and outcomes of patients with chronic lymphocytic leukemia (CLL). Half of the patients were managed with a watch and wait strategy, while the remainder-initiated treatment after a median follow-up of two point two months. Binet staging emerged as a key determinant for initiating therapy, with significantly higher treatment rates observed in patients with advanced-stage disease.

While high-risk molecular features such as unmutated IGHV and TP53 alterations were more frequently associated with treatment, these trends did not reach statistical significance in our cohort, likely reflecting sample size limitations. Comorbidity burden, as assessed by the Charlson Comorbidity Index, did not significantly impact the decision to treat, suggesting that treatment selection may be increasingly influenced by the availability of targeted therapies with favorable safety profiles.

These findings emphasize the importance of integrating clinical staging with molecular profiling in guiding therapeutic decisions and underscore the need for larger prospective studies to validate risk-adapted management strategies in CLL.

Ethics Statement and Conflict of Interest Disclosures

Financial support and sponsorship: All authors have declared that no financial support was received from any organization for the submitted work.

Ethics Consideration

The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national laws. Written informed consent was provided by all participants in this study.

Conflict of interest:

No known conflict of interest correlated with this publication.

Availability of data and materials

The data used and/or analyzed throughout this study are available from the corresponding authors upon reasonable request.

Competing interest

The authors declared that they have no competing interests.

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