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ORIGINAL ARTICLE

Clinical-epidemiological profile of patients with chronic lymphocytic leukemia in a public hospital in Rio de Janeiro - A retrospective cohort

Perfil clínico-epidemiológico de pacientes com leucemia linfocítica crônica em um hospital público do Rio de Janeiro - Uma coorte retrospectiva

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ABSTRACT

Introduction: Chronic lymphocytic leukemia (CLL) is the most common adult leukemia. In Brazil, clinical and epidemiological data are scarce. Ethnic diversity and unequal healthcare access may affect disease presentation and outcomes. **Objective:** To describe the clinical-epidemiological profile of CLL patients at a Brazilian university hospital. **Methods:** Retrospective study of CLL patients diagnosed from 2001 to 2022 in Rio de Janeiro. Data included gender, age, diagnosis year, symptoms, staging, mutational analysis (17p deletion, IGHV, TP53 mutations), treatment, and follow-up. Survival was calculated by age and Rai stage using Kaplan-Meier. **Results:** Among 41 cases, the mean diagnosis age was 66 years, with a higher prevalence in women (56.41%). Only 38.46% were asymptomatic, with lymphadenopathy as the most common sign. Most were Rai 0/Binet A and followed a watch-and-wait approach. Only 25.64% underwent mutational status analysis, and among those with an IGHV mutation, 75% followed a watch-and-wait strategy. In the survival analysis, patients aged ≤ 60 years and those classified as Rai stage 0 had a longer average follow-up time. **Conclusion:** Most patients were women, with a mean age of 66. Despite early-stage predominance, most were symptomatic. Survival interpretation was limited by few events but aligned with CLL natural history. Although most patients followed a watch-and-wait strategy, those requiring chemotherapy often needed more than one line of treatment, and only a few had their mutational status analyzed.Additionally, there were significant difficulties in accessing first-line medications through the Brazilian Unified Health System, which imposes barriers to treatment and may significantly compromise patient prognosis.

Keywords: Leukemia, lymphocytic, chronic, B-Cell; Lymphocytosis; Epidemiology.

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RESUMO

Introdução: A leucemia linfocítica crônica (LLC) é a leucemia mais comum em adultos. No Brasil, dados clínico-epidemiológicos são escassos. Fatores como diversidade étnica e desigualdade no acesso à saúde podem influenciar a apresentação e os desfechos da doença. **Objetivo:** Descrever o perfil clínico-epidemiológico de pacientes com LLC em hospital universitário brasileiro. **Métodos:** Estudo retrospectivo com pacientes diagnosticados com LLC entre 2001 e 2022 no Rio de Janeiro. Foram coletados dados sobre gênero, idade, ano do diagnóstico, sintomas, estadiamento, análise mutacional (deleção 17p, IGHV, mutações TP53), tratamento e seguimento. A sobrevida foi calculada por faixa etária e estágio Rai pelo método Kaplan-Meier. **Resultados:** Entre 41 pacientes, a maioria eram mulheres (56,41%) e a idade média ao diagnóstico foi 66 anos. Apenas 38,46% eram assintomáticos, com linfadenopatia como sinal mais comum. A maioria era Rai 0/Binet A, e tiveram conduta expectante. Apenas 25,64% foram submetidos à análise do status mutacional e, entre aqueles com mutação no IGHV, 75% tiveram conduta expectante. Na análise de sobrevida, pacientes com até 60 anos e estágio Rai 0 apresentaram maior tempo médio de acompanhamento. **Conclusão:** A maioria dos pacientes foram mulheres, com idade média de 66 anos. Apesar do predomínio de estágios iniciais, a maioria era sintomática. A interpretação da sobrevida foi limitada pelo baixo número de desfechos, embora os resultados estejam alinhados à história natural da LLC. Embora a maioria dos pacientes terem seguido uma conduta expectante, aqueles que necessitaram de quimioterapia frequentemente precisaram de mais de uma linha de tratamento, e poucos tiveram seu status mutacional analisado. Destaca-se, ainda, a dificuldade de acesso a medicamentos de primeira linha no Sistema Único de Saúde, o que impõe barreiras ao tratamento, podendo comprometer significativamente o prognóstico.

Palavras-chave: Leucemia linfocítica crônica de células B; Linfocitose; Epidemiologia.

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is a hematologic neoplasm characterized by the clonal proliferation of CD19+ B lymphocytes, with coexpression of CD5 and CD23[1]. It is the most common leukemia in adults[1-3], with a predominance in males and a median age at diagnosis of 70 years[1,2,4,5].

In most cases, the diagnosis is incidental through laboratory tests showing increased lymphocyte counts. However, CLL can also present with anemia, lymphadenopathy, splenomegaly, B symptoms (fever, weight loss, and night sweats), hemorrhages, or infections[1,3,5,6]. Regarding the clinical course, most patients experience an indolent progression with a delayed need for treatment and prolonged survival. However, some develop an aggressive form that requires early treatment and is associated with frequent relapses[1,5,7].

Treatment and life expectancy depend on clinical staging, assessed by the Rai and Binet classifications, which are based on blood cell counts and physical examination, and prognostic factors such as serum β2-microglobulin levels, immunoglobulin heavy chain (IGHV) mutation, TP53 mutation, and 17p deletion also influence prognosis[1-4,6,7]. Survival is approximately 13 years for low-risk patients (Rai 0, Binet A) and 2 to 3 years for high-risk cases (Rai III or IV, Binet C)[1,8,9]. While low-risk patients are often managed with a watch-and-wait approach, high-risk patients or those with mutations linked to poor prognosis may require chemotherapy, Bruton tyrosine kinase (BTK) inhibitors, BCL-2 inhibitors, or other targeted therapies[3,4,6].

Although several studies on CLL exist, data on the clinical-epidemiological profile of the disease in Brazil remain scarce. The Brazilian population is highly multiethnic, with socioeconomic disparities and unequal access to healthcare[10,11], actors that may influence disease presentation and outcomes.

Therefore, this study aims to describe the clinical-epidemiological profile of CLL patients followed at the hematology outpatient clinic of a university hospital in Rio de Janeiro between 2001 and 2022.

Methods

This is a retrospective cohort study conducted through the analysis of medical records of patients with a confirmed diagnosis of CLL by immunophenotyping by flow cytometry, between 2001 and 2022, at the hematology outpatient clinic of a university hospital in Rio de Janeiro.

The collected data included gender, age at diagnosis, year of diagnosis, signs and symptoms at diagnosis, Rai and Binet staging at diagnosis, whether mutational analysis was performed (presence of 17p deletion, IGHV mutation, and TP53 mutations), established treatment approach, need for more than one line of chemotherapy, and follow-up. Patients with incomplete data were excluded. Microsoft Excel was used for data tabulation, and R studio for calculating survival stratified by age group and Rai group (Kaplan-Meier), and graphical representation.

Data collection began after the study was approved by the local Research Ethics Committee (CEP) (approval number 4.431.763).

Results

Medical records of 41 patients were analyzed, with two being excluded due to incomplete data. Thus, the final sample included 39 patients (Table 1), of whom 22 (56.41%) were female and 17 (43.59%) were male. The mean age at diagnosis was 66 years, ranging from 42 to 90 years. There were 13 patients (33.33%) under 60 years old, 14 (35.90%) between 61 and 70 years old, and 12 (30.77%) over 70 years old. Only one patient (2.56%) was under 45 years old (Table 1).

As for clinical manifestations, 17 patients (43.59%) presented only lymphadenopathy at diagnosis, while 4 (10.26%) had exclusively B symptoms. Three patients (7.69%) had lymphadenopathy associated with B symptoms, and 15 (38.46%) were asymptomatic, with the diagnosis suspected based on a complete blood count performed for other reasons.

For prognostic classification, according to the Rai staging system, 14 patients (35.90%) were in stage 0, 12 (30.77%) in stage I, 6 (15.38%) in stage II, 4 (10.26%) in stage III, and 3 (7.69%) in stage IV. According to the Binet system, 24 patients (61.54%) were in stage A, 8 (20.51%) in stage B, and 7 (17.95%) in stage C.

Among the Rai stage 0 patients at diagnosis, one (7.14%) underwent chemotherapy at some point. Among those in Rai stage I, 4 (33.33%) received chemotherapy at some point. In Rai stage II, 2 (33.33%) underwent chemotherapy. All patients in Rai stages III and IV received chemotherapy. According to the Binet classification, among stage A patients, 4 (16.67%) underwent chemotherapy at some point. Among Binet stage B patients, 3 (37.50%) received chemotherapy, while all patients in Binet stage C underwent chemotherapy. Among those who required more than one line of chemotherapy, the majority (37.5%; n = 3) were diagnosed in Rai stage III/Binet C.

Regarding mutational status, only 10 patients (25.64%) were tested. Among them, all had IGHV mutation analysis, with 4 (40.0%) testing positive. Six patients (15.39%) were tested for TP53 mutation, all with negative results, and 3 (7.69%) for 17p deletion, with 2 (66,67%) testing positive.

Among patients with mutated IGHV, 3 (75.0%) were managed expectantly, and 1 (25.0%) received chemotherapy. Among the three patients tested for 17p deletion, all were managed expectantly.

As for treatment, 25 patients (64.10%) were managed expectantly, while 14 (35.90%) received chemotherapy at some point. Among those who received chemotherapy, 8 (57.14%) required more than one line of treatment. Of these, only 1 (12.50%) had a mutational status assessment. Among the 6 patients treated with a single chemotherapy regimen, 4 (66.67%) had their mutational status analyzed.

The therapeutic protocols used included RFC (Rituximab, Fludarabine, and Cyclophosphamide), CLB (Chlorambucil), R-CLB (Rituximab and Chlorambucil), CHOP (Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone), OFC (Obinutuzumab, Fludarabine, and Cyclophosphamide), RCOP (Rituximab, Cyclophosphamide, Vincristine, and Prednisone), COP (Cyclophosphamide, Vincristine, and Prednisone), RCTx (Rituximab and Cyclophosphamide), as well as Dexamethasone and Prednisone.

Regarding the current follow-up status, 7 patients (17.95%) are in remission, 30 (76.92%) remain under chemotherapy or expectant management, one abandoned follow-up, and one (2.56%) died. Finally, there was a single case of transformation to Richter's Syndrome (2.56%) (Figure 1).

In the survival analysis stratified by age group, the highest survival rates were observed in the ≤ 60 years and 61–70 years groups, as the only death recorded occurred in a patient over 70 years old. Thus, the difference in survival between the groups was not statistically significant (p value 0.28) (Figure 2). The analysis of follow-up time by age group showed that patients aged ≤ 60 years had the longest average follow-up time (1952 days) and the highest median (1242 days), with a maximum of 7669 days. Patients aged between 61 and 70 years had an average follow-up time of 1818 days and a median of 802 days, while the > 70 years

Table 1. Clinical and epidemiological data of patients diagnosed with chronic lymphocytic leukemia, followed up at the hematology outpatient clinic, from 2001 to 2022.

Gender	Year of diagnosis	Age at diagnosis (years)	Adenomegaly	Symptoms B	Stage	17p deletion	IGHV mutation	TP53 mutation	Treatment	> 1 line of treatment	Follow-up
M	2019	57	no	no	Rai 0/ Binet A	no	yes	-	Expectant	-	Under follow-up
M	2005	58	no	no	Rai 0/ Binet A	yes	no	-	Expectant	-	Under follow-up
F	2018	48	yes	no	Rai I/ Binet A	-	-	-	Expectant	-	Under follow-up
M	2017	51	yes	no	Rai I/ Binet A	-	-	-	Expectant	-	Under follow-up
F	2021	90	yes	no	Rai I/ Binet A	-	-	-	Expectant	-	Under follow-up
F	2020	54	no	yes	Rai 0/ Binet A	-	-	-	Expectant	-	Under follow-up
M	2022	71	yes	no	Rai 0/ Binet A	-	-	-	Expectant	-	Under follow-up
M	2017	54	yes	yes	Rai II/ Binet B	-	-	-	Chemotherapy	no	Under follow-up
F	2021	69	yes	no	Rai I/ Binet B	-	-	-	Expectant	-	Under follow-up
F	2019	62	yes	no	Rai 0/ Binet A	-	-	-	Expectant	-	Under follow-up
M	2018	76	yes	no	Rai I/ Binet B	-	-	-	Chemotherapy	no	Death
F	2021	66	no	yes	Rai 0/ Binet A	-	-	-	Expectant	-	Under follow-up
F	2021	53	yes	yes	Rai II/ Binet B	-	-	-	Expectant	-	Under follow-up
F	2021	71	no	no	Rai 0/ Binet A	-	-	-	Expectant	-	Under follow-up
F	2016	80	no	no	Rai 0/ Binet A	-	-	-	Expectant	-	Under follow-up
M	2021	71	no	no	Rai 0/ Binet A	-	-	-	Expectant	-	Under follow-up
M	2005	64	no	no	Rai 0/ Binet A	-	-	-	Chemotherapy	yes	Complete remission
M	2019	68	yes	no	Rai III/ Binet C	-	no	no	Chemotherapy	yes	Under follow-up
M	2018	54	yes	no	Rai I/ Binet A	-	-	-	Expectante	-	Under follow-up
M	2019	50	yes	yes	Rai I/ Binet B	-	no	no	Chemotherapy	no	Complete remission
M	2022	74	no	no	Rai 0/ Binet A	-	-	-	Expectant	-	Under follow-up

F	2021	71	yes	no	Rai II/ Binet A	-	-	-	Expectant	-	Under follow-up
M	2021	80	no	no	Rai 0/ Binet A	-	-	-	Expectant	-	Under follow-up
F	2020	63	yes	no	Rai I/ Binet B	yes	no	-	Expectant	-	Under follow-up
M	2021	68	no	no	Rai II/ Binet A	-	-	-	Expectant	-	Under follow-up
F	2022	85	no	yes	Rai IV/ Binet C	-	yes	no	Chemotherapy	no	Under follow-up
F	2016	77	no	no	Rai II/ Binet A	-	-	-	Chemotherapy	yes	Complete remission
F	2010	71	no	yes	Rai III/ Binet C	-	-	-	Chemotherapy	yes	Complete remission
F	2005	67	no	no	Rai III/ Binet C	-	-	-	Chemotherapy	yes	Under follow-up
F	2019	58	yes	no	Rai I/ Binet B	-	yes	no	Expectant	-	Under follow-up
F	2019	71	no	no	Rai 0/ Binet A	-	yes	-	Expectant	-	Under follow-up
F	2011	78	yes	no	Rai I/ Binet A	-	-	-	Chemotherapy	yes	Complete remission
F	2022	70	yes	no	Rai III/ Binet C	-	no	no	Chemotherapy	no	Under follow-up
M	2018	74	yes	no	Rai II/ Binet A	-	-	-	Expectant	-	Treatment abandonment
F	2020	42	yes	no	Rai I/ Binet B	-	-	-	Expectant	-	Under follow-up
M	2019	53	yes	no	Rai I/ Binet A	-	no	no	Chemotherapy	no	Complete remission
M	2001	56	no	no	Rai IV/ Binet C	-	-	-	Chemotherapy	yes	Complete remission
F	2019	47	no	no	Rai 0/ Binet A	-	-	-	Expectant	-	Under follow-up
F	2014	63	no	no	Rai IV/ Binet C	-	-	-	Chemotherapy	yes	Under follow-up

Caption: F = Female; M = Male.

group had the shortest average (997 days) and median (438 days) follow-up times.

The same pattern was observed in the survival analysis stratified by Rai classification, in which the only death occurred in a Rai I patient, with no statistically significant difference in survival between the groups (p value 0.78) (Figure 3). The analysis of patient follow-up time showed that the Rai 0 group had the longest average follow-up time, with approximately 1975 days (median of 1217 days). The intermediate groups, Rai I and Rai II, presented similar average follow-up times of around 1410 and 1385 days, respectively. Patients classified as Rai III and Rai IV had the shortest average follow-up times, close to 1140 and 1090 days.

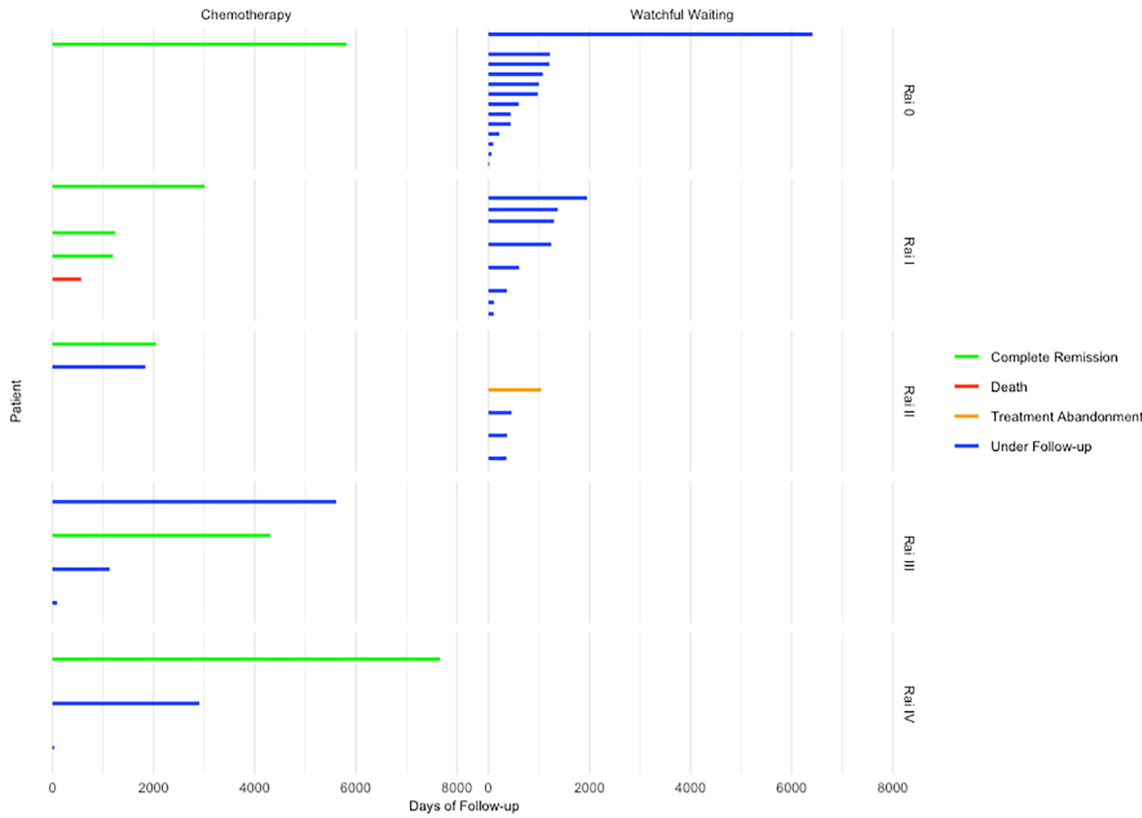

Figure 1. Follow-up time in days and outcomes of patients diagnosed with chronic lymphocytic leukemia followed at the hematology outpatient clinic from 2001 to 2022, according to treatment and Rai group.

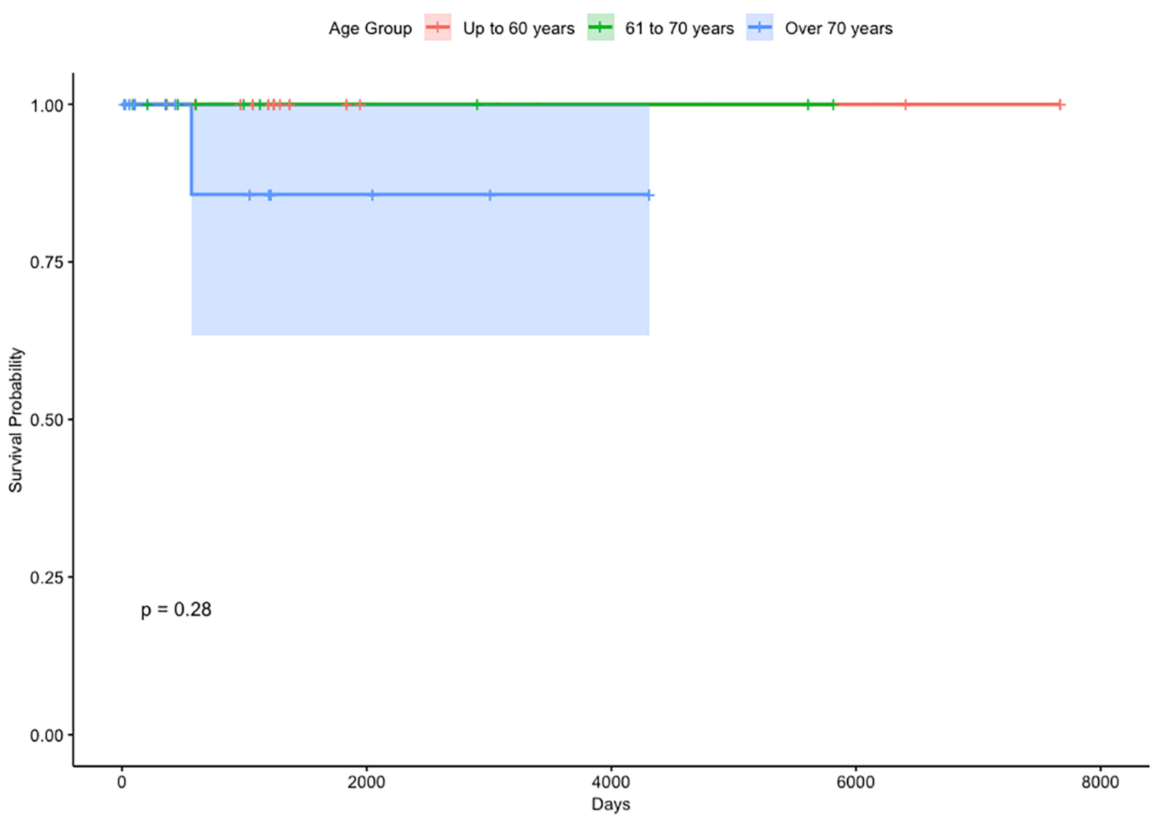

Figure 2. Kaplan-Meier survival curve stratified by age group of patients with chronic lymphocytic leukemia, followed up at the hematology outpatient clinic from 2001 to 2022.

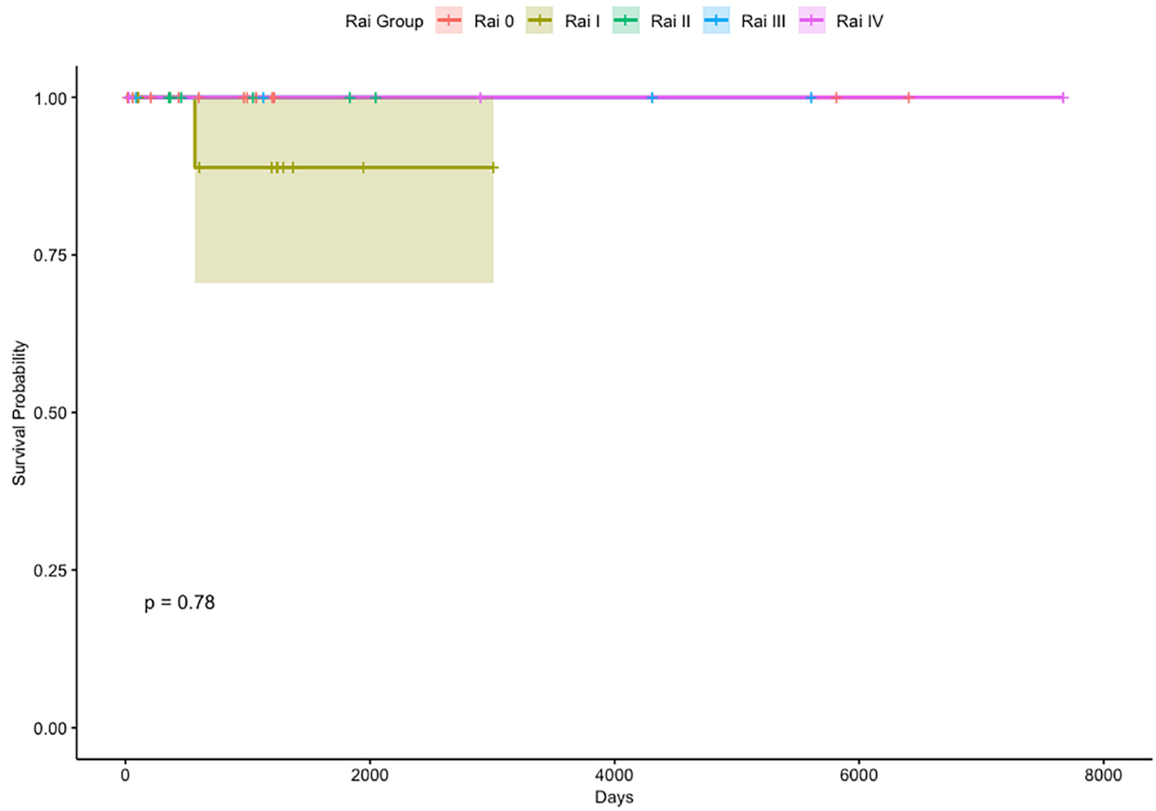

Figure 3. Kaplan-Meier survival curve stratified by Rai group, of patients with chronic lymphocytic leukemia followed up at the hematology outpatient clinic, from 2001 to 2022.

Discussion

Regarding epidemiology, the results of this study indicate a higher prevalence of female patients compared to male patients, which differs from the American literature, where the male-to-female ratio is reported as 1.9:1[1,2,4,5,12].However, despite Brazilian studies also indicating a higher incidence in men, this difference is smaller (60–56%)[10,11]. A possible explanation for this discrepancy may be life expectancy in Brazil, which is 79 years for women and 73 years for men[13], contrasting with developed countries — where most studies on CLL are conducted — where the longevity gap between sexes is smaller[14]. Additionally, the higher number of diagnoses in women in Brazil may be attributed to the fact that women tend to take better care of their health and seek medical services more frequently, leading to a higher rate of diagnosis[15,16]. It is also important to consider that the small sample size in this study may have influenced these findings.

The average age at diagnosis was 66 years, which is lower than what is reported in most international studies[1,2,4,5,12], but aligns with recent retrospective studies conducted in Brazil[10,11] and Latin America[13,14], which describe an average of 65 to 66 years. This trend has also been observed in other countries, with an increasing incidence of CLL in younger individuals. Recent studies indicate that nearly 15% of patients are diagnosed at 55 years or younger[1], and in this study, this age group represented 21.95% of cases.

Unlike the literature, which reports that most patients are asymptomatic at diagnosis[1,3,5,6], in this study, 61.54% of patients presented with lymphadenopathy, B symptoms, or both at the time of diagnosis, suggesting a more advanced disease[1]. However, most patients were still in the early stages of the disease (Binet A/Rai 0), while only a minority were classified as Binet C/Rai IV, consistent with other studies[11]. This apparent discrepancy may be related to the fact that the Binet and Rai classifications do not consider B symptoms, which were reported by 10.26% of patients. A study conducted in São Paulo found similar data, with 54.8% of patients presenting with lymphadenopathy at diagnosis[10]. This profile may be explained by the fact that patients in the Brazilian public healthcare system (SUS) face prolonged delays before reaching specialized care in university hospitals, requiring initial suspicion and referral from Primary Health Care, which is regulated and can lead to diagnosis at more advanced stages.

In the survival analysis stratified by age group, patients aged ≤ 60 years showed a longer mean and median follow-up time compared to the other age groups, in line with the literature, which reports better survival in this group[17]. Since there were no deaths in this stratum and the follow-up period was longer, the Kaplan-Meier curve extended further along the X-axis, reflecting a longer event-free (death) time. However, this result does not necessarily indicate a lower risk of death, but rather a longer follow-up time without the occurrence of the outcome. This behavior is expected in studies with few events and unequal follow-up periods between groups.

The same applies to the survival analysis stratified by Rai classification. Patients with Rai stage 0 had the longest average follow-up time (5.4 years), followed by the Rai I (3.9 years) and Rai II (3.8 years) groups, with similar durations, while Rai III (3.1 years) and Rai IV (3.0 years) had the shortest follow-up times. Although these results suggest better survival in the early stages of the disease, it is important to highlight that there was only one death (in a Rai I patient), which limits the interpretation of overall survival. The follow-up times reflect more the event-free time (death) rather than actual differences in the probability of death between Rai groups. Nonetheless, this pattern is consistent with the natural history of CLL, in which patients at Rai stage 0 typically follow a more indolent course with longer survival, while survival drops to 2–3 years in high-risk cases (Rai III or IV, Binet C)[1,8,9].

In addition to clinical staging, performed using the Rai and Binet classifications, the definition of treatment and prognosis in CLL currently includes a range of laboratory and genetic biomarkers. Among the most relevant factors are 17p deletion, TP53 gene mutation, and IGHV mutation. The presence of 17p deletion and/or TP53 gene mutation is associated with resistance to conventional therapies and a worse prognosis, whereas patients with somatic IGHV mutations tend to have a more favorable clinical course[1-4,6,7]. In this study, only 25.64% of patients had their mutational status assessed, with most being tested only for the IGHV mutation. A Brazilian study conducted in 2017 with 1,903 patients showed that only 16% were evaluated for cytogenetic abnormalities[11]. In contrast, an American study demonstrated that fluorescence in situ hybridization (FISH) analysis was performed in 49.3% of cases[15]. This difference may be explained by the limited access to these tests in Brazil through the SUS and financial constraints that prevent many patients from undergoing them in the private sector.

Regarding IGHV mutation frequency, the American literature reports its presence in 32.3% of patients[15], a value similar to that found in this study. However, the 17p deletion is typically identified in 11.9% of cases[18], a percentage significantly higher than that observed in the studied population. This discrepancy may be due to the small number of patients tested for genetic alterations.

Most patients classified as Rai 0, I, and II or Binet A and B did not require long-term chemotherapy and were managed with a watch-and-wait approach. On the other hand, all patients classified as Rai III and IV or Binet C received chemotherapy treatment, in accordance with literature recommendations[3,4,6]. Among the patients treated even in early stages, the main factors indicating the need for therapy were the presence of B symptoms, bulky or compressive lymphadenopathy, or a significant increase in lymphocytosis, as well as disease progression over the years, reaching criteria for treatment initiation. According to the literature, approximately one-third of patients develop signs and symptoms requiring treatment[1], a finding that corroborates the data from this study, in which 35.90% of patients underwent chemotherapy at some point.

Among the patients who required only one line of chemotherapy, 66.7% underwent mutational status testing. Conversely, among those who received more than one line of treatment, only 12.5% had this analysis performed, highlighting the relevance of mutational studies in therapy selection. Ideally, all patients eligible for treatment should undergo a prognostic evaluation with molecular biology tests, as these analyses are now fundamental in defining the best therapeutic approach[19].

Richter's transformation was observed in only one patient (2.56%), a finding consistent with the literature, which reports a prevalence of 2% to 6%[20]. Additionally, only one death was recorded among the monitored patients, reflecting the indolent nature of CLL[1].

Regarding the treatment used, it was found that not all patients received the first-line therapy recommended in the literature. Traditional chemotherapy with alkylating agents and/or nucleoside analogs achieves complete remission in up to 30% to 40% of patients, whereas combinations of monoclonal antibodies with chemotherapeutic agents increase this number to 60% to 70%[21]. In this study, some patients received chemotherapy alone, while others received chemotherapy combined with a monoclonal antibody, and 50% of the patients achieved complete remission, supporting the data in the literature.

Treatment approaches for CLL have changed rapidly in recent years with the emergence of targeted therapies, which have been shown to improve survival and cause fewer side effects compared to conventional chemotherapy-based treatment[19]. Currently, for most patients, especially those with high-risk CLL—such as those with 17p deletion and/or TP53 mutations—therapies with BTK inhibitors and BCL-2 antagonists are preferred over chemoimmunotherapy[19]. However, none of the patients in this study received these medications, even when indicated. This is largely due to the difficulty in accessing BTK inhibitors, BCL-2 antagonists, or other targeted therapies through the SUS. The National Commission for the Incorporation of Technologies (CONITEC) initially recommended against incorporating ibrutinib into the SUS for treating CLL patients ineligible for purine analog treatment, with the only justification for the unfavorable recommendation being economic reasons[22]. Venetoclax is also not included in the list of drugs mandated for SUS coverage[23]. Therefore, patients must still resort to legal action to gain access to these treatments.

One of the limitations of this study was the small number of patients. Additionally, because this is an indolent disease, only one death was recorded, which made survival analysis difficult. Another relevant limitation was the low number of patients who underwent mutational status assessment.

Conclusion

Regarding epidemiological data, this study highlighted characteristics that differ from international data. The average age at diagnosis was consistent with Brazilian and Latin American data. Additionally, a higher prevalence of female patients was observed, possibly influenced by the life expectancy of the Brazilian population and the fact that women seek healthcare services more frequently, leading to a higher rate of diagnosis, in addition to the small sample size of this study.

Most patients presented symptoms at diagnosis, which may be related to the prolonged time between disease onset and specialized referral within the SUS. Despite this, most were still classified in early stages (Binet A/Rai 0) and managed with a watch-and-wait approach.

In the survival analysis, patients aged ≤ 60 years and those classified as Rai stage 0 had a longer average follow-up time. However, the low number of deaths limits the interpretation of overall survival, although the results are consistent with the natural history of CLL.

Furthermore, access to essential tests for prognosis and therapeutic decision-making, such as mutational status analysis and cytogenetic tests, was limited, making proper risk stratification difficult. Additionally, limited access to first-line drugs in the SUS imposes further barriers to initial treatment and may significantly impact patient prognosis.

Authors' Contributions:

We describe contributions to the papers using the taxanomy (CRediT) provided above: *Conceptualization, Investigation, Methodology, Visualization & Writing – original draft*: TPF do Nascimento TPF; GLV Moraes; GF Avila. *Project Administration & Supervision*: KG Frigotto; ICR Diogo; EB Riscarolli. *Writing – review & editing*: MC Magalhães; VRGA Valviesse.

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