Original Article

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Quick Response Code:

Website: www.ijhonline.org

DOI: 10.4103/ijh.ijh_23_21

The significance of Rai and Binet clinical staging on the survival of chronic lymphocytic leukemia patients in the Kurdistan region of Iraq

Shlan S. Muhammad, Ahmed Khudair Yassin[1], Rawand P. Shamoon[2], Nawsherwan S Mohammed[2], Marwa Nadhim Nadhim, Kawa M Hassan[1], Bryar Sabah Rashid[3], Shokhan M Mohammad, Ranan karadagh[2], Ghanim S Numan, Lara Lateef Abdulrahman, Sana D Jalal[4], Zhala O. Ahmed[3], Hisham A. Getta[4], Tavan I. Mahmood[3], Basil K. Abdulla[5], Dana A. Abdullah[4], Rozh-hat A. Yousif[6], Zeki A. Mohamed[7]

Department of Adult Hematology, Nanakali Hospital, Erbil, [1]Department of Internal Medicine, College of Medicine, Hawler Medical University, [2]Department of Pathology, College of Medicine, Hawler Medical University, [3]Department of Adult Hematology, Hiwa Hospital for Blood Disease, Sulaymaniyah, [4]Department of Pathology, College of Medicine, University of Sulaymaniyah, Sulaymaniyah, [5]Department of Hematology, Hiwa Cancer Hospital, Sulaymaniyah, [6]Department of Adult Hematology-Azadi Centre for Blood Disease, [7]Department of Medicine, College of Medicine, University of Duhok, Duhok, Kurdistan Region, Iraq

Address for correspondence:
Dr. Shlan S. Muhammad, Nanakali Hospital, Erbil, Iraq.
E-mail: shlan.mohammed@yahoo.com

Submission: 07-06-2021
Revised: 04-07-2021
Accepted: 06-07-2021
Published: 01-12-2021

Abstract:

BACKGROUND: Chronic lymphocytic leukemia is an uncommon type of leukemia in Iraq, although many reported cases of chronic lymphocytic leukemia in the Iraqi Kurdistan region are of high risk stage. Staging of chronic lymphocytic leukemia is essential in treatment planning and for disease prognosis. the aims of this study were to find out the difference in patients' survival with early and late clinical stages, and to evaluate CLL outcome in relation to the Rai and Binet staging.

PATIENTS AND METHODS: This retrospective cross-sectional analysis studied 250 patients, 170 male and 80 female, with chronic lymphocytic leukemia who were registered in three hemato-oncology centers in Iraqi Kurdistan for the last 10 years. The diagnosis of the disease was made according to the guideline of the International Workshop Chronic Lymphocytic Leukemia update of the National Cancer Institute. The patients' clinical staging was determined by a senior hematologist based on the clinical and laboratory findings.

RESULTS: The mean age of the patients was 63(±11.8) years, 40% were >65 years. The median survival was 27 months. Elderly patients >65 years had significantly lower mean survival. The Rai staging was distributed as follows: stage 0 (24.8%), stage I (12.8%), stage II (30.8%), stage III (9.6%) and stage IV (22%). The median survival was significantly higher among patients with Rai stage 0 comparing to patients with advanced stages (P<0.001). The Binet stage was distributed as follows: stage A (47.2%), stage B (26.4%) and stage C (26.4%). The median patients' survival was significantly higher among patients with Binet stage A comparing to those with Binet stage C (P<0.001).

CONCLUSIONS: The survival of patients with chronic lymphocytic leukemia strongly related to the clinical stages of both staging systems.

Keywords:

Binet staging, chronic lymphocytic leukemia, rai staging, survival

Introduction

Chronic lymphocytic leukemia (CLL) is known as lymphproliferative disorder recognized with accumulated small lymphocytes at lymph nodes, bone marrow, blood, liver, spleen, or often at other organs. These lymphocytes are marked with mature morphology and immature biology. Mostly, CLL is defined as clonal growth of B-cells and in less frequency accompanied (removed) with T-cells (type).[1] CLL represented about

How to cite this article: Muhammad SS, Yassin AK, Shamoon RP, Mohammed NS, Nadhim MN, Hassan KM, *et al*. The significance of Rai and Binet clinical staging on the survival of chronic lymphocytic leukemia patients in the Kurdistan region of Iraq. Iraqi J Hematol 2021;10:146-51.

one-third of adult leukemia types,[2] with a median age at the diagnosis of 65–70 years.[3] CLL is also recorded at younger age population (<55 years) with prevalence rates ranging between 20% and 30% of patients.[4]

Diagnosis of CLL is done through observation of high level of monoclonal B-lymphocytes in the peripheral blood that is confirmed by flow cytometry and blood smear examination which showed lymphocyte cells morphology of CLL, in addition to large atypical lymphocytes seen in some cases (put it behind, is done).[5] CLL is also presented with splenomegaly, hepatomegaly, lymphadenopathy, and classical clinical features such as fatigue, fever, weight loss, and sweating.[6] The treatment of CLL patients at early stage or low risk includes only wait and watch with regular monitoring, while the treatment of CLL patients at advanced stage or high risk includes treating symptomatic active CLL disease with chemo-immunotherapy, chemotherapy, targeted therapy, and others depending on the physical status of patients, comorbidities, treatment response, and relapses.[7,8]

In purpose of CLL staging, (removed) two clinical staging systems were applied for planning of treatment and prediction of survival of CLL patients.[9,10] These clinical staging systems are dependable on clinical history, physical examination, complete and differential blood count, serum chemistry, and bone marrow examination (in some cases).[9,10] The Rai staging which is widely used in the United States included five subgroups; Stage 0 (lymphocytosis only) that is arranged into low-risk group, Stage I (lymphocytosis and lymphadenopathy), Stage II (lymphocytosis and hepatomegaly and/or splenomegaly with/without lymphadenopathy) that are arranged into intermediate-risk group, Stage III (lymphocytosis and anemia with/without lymphadenopathy/organomegaly), and Stage IV (lymphocytosis and thrombocytopenia with/without lymphadenopathy/organomegaly) that are arranged into high-risk group.[9] The Binet staging system is highly applied in European countries, and it includes three groups; Stage A (hemoglobin ≥10.0 g/dl, platelets count ≥100 × 10^9/l, <3 lymph nodes), Stage B (hemoglobin ≥10.0 g/dl, platelets count ≥100 × 10^9/l, ≥3 lymph nodes), and Stage C (hemoglobin <10.0 g/dl and platelets count <100 × 10^9/l).[10] The survival of patients with CLL is varied according to the staging of the disease as for patients with Rai 0 or Binet A, it was with average of >10 years, for CLL patients with Rai I and II or Binet B, the average survival reached >8 years, while for CLL patients with Rai III and IV or Binet C, the average survival reached to about 6.5 years.[11] However, with advancing facilities in the management of CLL and novel treatments in the past years, the overall survival of CLL patients had been improved.[12] In addition, many markers are available nowadays for the prediction of CLL prognosis, especially at earlier stages.[11,13] (either removed or replaced because it is unrelated to the above).

CLL is a hematological tumor characterized by a variable prognosis with some cases having rapid progressive course and others with indolent disease. However, the survival of CLL is ranging between five to ten years.[14,15] Longer survival duration of CLL patients in developed countries might be related to the better quality of life, in addition to improved diagnostic techniques, and advancement in treatment regimens with better efficacy and higher safety.[16-18] In spite of this improvement in diagnosis, treatment and forecasting of CLL in last decades, the survival of patients with CLL is still variable especially among newly diagnosed patients.[19] CLL is the least frequent type of leukemias in Iraq.[20] In the northern Kurdistan region however, about half of the diagnosed cases are at advanced risk.[21] Moreover, national researches studying the effect of CLL disease staging on survival of patients are scarce. Hence, this study aimed to find out the important differences in the survival between early and late clinical stages and difference in survival between Rai and Benet staging among CLL patients in this geographical area.

Patients and Methods

This retrospective cross-sectional study conveniently reviewed 250 CLL patients who have been diagnosed or referred to the three hemato-oncology centers in the Kurdistan region of Iraq, namely Nanakali Hospital in Erbil, Hiwa Hospital in Sulaimaniyah, and Azadi Hospital in Duhok through the duration of period from January 2010 to January 2020.

The diagnosis of CLL was decided according to criteria set by the International Workshop on CLL (iwCLL).[22] All patients had flow-cytometry and/or immunohistochemistry at time of presentation. Patients with small lymphocytic leukemia (SLL), monoclonal B cell lymphocytosis of <5000/mm^3, Richter's syndrome and B-cell prolymphocytic leukemia were not included. Moreover, CLL patients with incomplete data or disease duration of less than one year were excluded also.

The study has been implemented in accordance with the Helsinki Declaration. Ethical approval was obtained from the Ethical Committee of the Kurdistan Board for Medical Specialties.

The authors used hospital records to retrieve patients' clinical and laboratory data in the three centers. Data were collected in a preprepared questionnaire.

Statistical analysis was done using Statistical Package of the Social Sciences software version 22 (Chicago, Illinois,

USA). The independent sample *t*-test was applied for analyzing two means, while one-way ANOVA analysis was used for the analysis of more than two means. Kaplan–Meier curve was used to assess the survival duration of CLL patients. Level of significance (*P* value) was regarded statistically significant if it was 0.05 or less.

Results

In this study, 250 CLL patients were included, of whom 100 (40%) were >65 years and 150 (60%) were ≤65 years. More than two-thirds of the patients were male (68%); the male-to-female ratio was 2.12:1. Eighteen patients (7.2%) had positive family history of CLL.

The overall median follow-up duration was 27 months. The mean survival of CLL patients >65 years was significantly lower ($P = 0.001$) than median survival of CLL patients with 65 years and less. The mean survival did not change significantly between males and females. Table 1 shows the details of relations of patients' general characteristics with survival.

At the time of presentation, lymphadenopathy was present in 78 (31.2%) patients. Splenomegaly and hepatomegaly were encountered in 40.8% and 22.8% of patients, respectively. Fourteen patients (5.6%) had lymphadenopathy with hepatosplenomegaly and eight (3.2%) had three or more lymph node areas enlargement at the time of presentation. The absolute lymphocyte count was $\geq 36 \times 10^9$/L in 120 (48%) patients. The hemoglobin level was <10 g/dL in 75 (30%) patients; while 80 patients (32%) had platelets count of $<100 \times 10^9$/L at diagnosis.

Table 2 illustrates the mean survival of CLL patients in relation to the clinical characteristics and laboratory data at the time of presentation. As shown in Table 2, patients with lymphocyte count $\geq 36 \times 10^9$/L (why you choose this no.??), lymphadenopathy, organomegaly, low hemoglobin, and low platelets counts had significantly shorter survivals.

The overall median survival of CLL patients was 27 months. As illustrated in Table 3 and Figures 1 and 2, patients with advanced disease stages had significantly lower survival comparing to patients who presented at early-stage disease. Table 4 shows the association of patients' age with CLL clinical stage at time of diagnosis.

Discussion

CLL is a common type of leukemia in the West and developed countries characterized by variable prognosis as many patients who are asymptomatic require no therapy while others can have progressive disease with need for urgent therapy.[5] Staging of CLL is helpful in planning for management strategy and for prognosis.[23]

In the current study, 250 CLL patients were conveniently included and their survival was scrutinized. Their mean age was 63 (±11.8) years, ranged between 35 and 91.8 years. The mean survival of those over 65 years with CLL was significantly lower, 28.8 ± 24.7 months, comparing to the mean survival of those ≤65 years of group, 39.1 ± 24.7 months ($P = 0.001$). This finding is consistent with the results of Parikh *et al*.,[24] who reported longer survival duration in CLL patients aged ≤55 years. Inconsistently, Ujjani *et al*.[25] found no effect of age on patients' survival treated by ibrutininb, although the mortality was significantly higher among older patients. In the current study, we found patients' age as an independent factor that is associated with the survival regardless the disease stage as illustrated in Table 4. Our

Table 1: Association of general characteristics of CLL patients with mean survival

Variable	*n* (%)	Mean survival (months)	*P*
Age (years), mean±SD (range)	63±11.8 (35-91.8)		0.001 (S)
≤65	150 (60.0)	39.1±24.7	
>65	100 (40.0)	28.8±20.9	
Gender			
Male	170 (68.0)	36.7±24.1	0.09 (NS)
Female	80 (32.0)	31.3±22.7	
BMI			
Not obese	223 (89.2)	33.9±23.2	0.03 (S)
Obese	27 (10.8)	43.9±27.1	
Family history of CLL			
No	232 (92.8)	35.1±24	0.7 (NS)
Yes	18 (7.2)	33.3±21.1	
Total	250 (100.0)		

CLL=Chronic lymphocytic leukemia, S=Significant, NS=Not significant, SD=Standard deviation

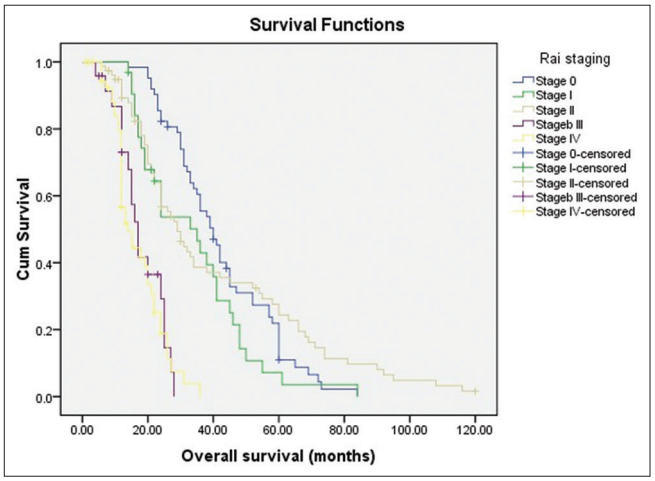

Figure 1: Kaplan–Meier curve of chronic lymphocytic leukemia patients according to Rai staging (blue = Stage 0, green = Stage I, brown = Stage II, burble = Stage III, yellow = Stage IV)

Table 2: Association of the mean survival with clinical and lab characteristics of CLL patients

Variable	*n* (%)	Mean survival (months)	*P*
Lymphadenopathy			
Yes	78 (31.2)	27.7±17.4	0.001 (S)
No	172 (68.8)	38.3±25.5	
Splenomegaly			
Yes	102 (40.8)	30.4±20.8	0.01 (S)
No	148 (59.2)	38.2±25.2	
Hepatomegaly			
Yes	57 (22.8)	28.9±16.7	0.03 (S)
No	193 (77.2)	36.5±25.3	
Lymphadenopathy, splenomegaly, and hepatomegaly			
Yes	14 (5.6)	20.2±10.1	0.005 (S)
No	236 (94.4)	34.3±18.7	
Three and more areas of lymph node enlargement			
Yes	8 (3.2)	30.5±17.5	0.5 (NS)
No	242 (96.8)	35±24	
Hemoglobin (g/dl)			
<10	75 (30.0)	25.5±10.2	<0.001 (S)
≥10	175 (70.0)	36.4±2.3	
Lymphocyte count			
$\geq 36\times10^3$	120 (48.0)	26.8±21.1	0.02 (S)
$<36\times10^3$	130 (52.0)	33±21.5	
Platelets			
$\geq 100\times10^9$	170 (68.0)	36.6±24.2	0.006 (S)
$<100\times10^9$	80 (32.0)	28.2±18.6	
Total	250 (100.0)		

S=Significant, NS=Not significant

Table 3: Association of median survival of CLL patients with Rai and Binet staging

Variable	*n* (%)	median survival (months)*	*P*
Rai staging			
Stage 0	62 (24.8)	40.0	<0.001 (S)
Stage I	32 (12.8)	35.0	
Stage II	77 (30.8)	29.0	
Stage III	24 (9.6)	17.0	
Stage IV	55 (22.0)	14.0	
Binet stages			
Stage A	118 (47.2)	38.0	<0.001 (S)
Stage B	66 (26.4)	24.0	
Stage C	66 (26.4)	15.0	
Total	250 (100.0)		

*Kaplan-Meier function. S=Significant, NS=Not significant

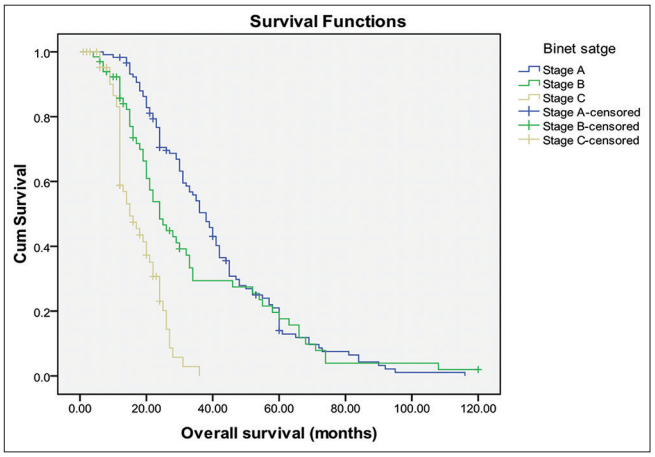

Figure 2: Kaplan–Meier curve of chronic lymphocytic leukemia patients according to Binet stages (blue = Stage A, green = Stage B, brown = Stage C)

study revealed also lower mean survival of obese CLL patients (P = 0.03). This finding is comparable to the results of Fürstenau *et al*.,[26] who studied the relation of CLL survival to the BMI in Germany reported that the impact of obesity on the survival of CLL patients is controversial.[24]

In the current cohort, nearly a quarter of CLL patients had Stage 0 disease and presented with lymphocytosis only. On the other hand, 79 patients (31.6%) fall in the high-risk group and presented with disease Stages III and IV. The proportion of patient with advanced disease was obviously high; comparable figures were reported by a previous study in the northern Kurdistan of Iraq.[21] Alawadi in a previous study conducted over CLL patients in Southern Iraq reported 14% CLL patients with Stages III and IV.[27] In the same study, however, 23.5% of the patients had Stage 0 disease which is comparable to our results. With the Binet staging system, nearly half of CLL patients had Stage A disease (47.2%), and the remaining patients equally fall in the disease Stages

Table 4: Association of patients' age with CLL clinical stage at time of diagnosis

Variable	Age at diagnosis		*P*
	≤65 years	>65 years	
Rai staging			
Stage 0	31 (20.0)	31 (31.0)	0.03 (S)
Stage I	26 (17.3)	6 (6.0)	
Stage II	43 (28.7)	34 (34.0)	
Stage III	13 (8.7)	11 (11.0)	
Stage IV	37 (24.7)	18 (18.0)	
Binet stages			
Stage A	71 (47.3)	47 (47.0)	0.14 (NS)
Stage B	34 (22.7)	32 (32.0)	
Stage C	45 (30.0)	21 (21.0)	

S=Significant, NS=Not significant

B and C (26.4% each). These findings are inconsistent with the results of the earlier from Erbil which reported 55.3% of CLL patients with Binet C.[21] This inconsistency might be attributed to differences in inclusion criteria, study population, and sample size. The Rai and Binet staging our CLL patients had relatively less advanced Rai and Binet clinical stages at time of diagnosis comparing to results of Bagheri *et al*.'s[28] study in Iran while worse than results of Weide *et al*.'s study in the UK.[29] The variation of clinical staging of CLL between different countries may due to variability in diagnostic technologies although the prevalence of CLL is higher in Western countries. The overall median survival of the CLL patients in the current study was 27 months; this was considerably higher when compared to the median survival of the two previous studies in Iraq[20,21] but lower than that reported from the Western world.[19]

The patients' survival inversely correlated with the disease stage. The median survival was significantly higher among patients with Rai Stage 0 and reduced steadily with the advancement of the stage. Similarly, patients with Binet Stage A had significantly longer survival. These findings are similar to the results of de Faria *et al*.[30] and Flowers *et al*.,[31] who reported that CLL patients with Rai Stage 0 and Binet Stage A had significantly longer survival, while patients with Rai Stage III or IV and Binet Stage C had significantly shorter survival. Both Rai and Binet systems are dependable on clinical and laboratory parameters which are critically affecting the survival of CLL patients;[32,33] however, many authors stated that the Binet staging system is clinically more relevant to the survival.[10,28] In the current cohort, we found comparable survival figures out of both staging systems.

The current study revealed that CLL patients with lymphadenopathy or splenomegaly had significantly shorter mean survivals comparing to the patients who had no lymphadenopathy or organomegaly. Those who had lymph node involvement with organomegaly did worse and had significantly shorter survival. These findings are in agreement with the results of Huang *et al*.'s[34] study in Taiwan. Moreover, our study showed that CLL patients with low hemoglobin level or higher lymphocyte count or low platelets count had significantly shorter survival (and this is reflect the advanced stage disease of these patients). These findings are close to results of Salawu *et al*.'s[35] study in Nigeria. These findings reveal the importance of the clinical parameters in staging of CLL and hence for prognosis and survival prediction.[36]

Conclusions

The survival of patients with CLL is significantly related to both clinical staging systems and laboratory data. This study urged the hematologists to adopt the clinical staging systems for the sake of prognosis of CLL patients.

Acknowledgment

Great thanks to all medical health staff working in cancer centers in Kurdistan for their efforts and help to complete my research.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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