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Impact of clinical staging and demographic data (age and sex) on response to treatment and survival of chronic lymphocytic leukemia patients in Kurdistan Region of Iraq

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

Department of Hematology, Hiwa Cancer Hospital, [1]Department of Pathology, College of Medicine, University of Sulaimani, [7]Department of Pathology, College of Medicine, University of Sulaymaniyah, Sulaymaniyah, Departments of [2]Medicine and [4]Pathology, College of Medicine, Hawler Medical University, [5]Department of Hematology, Nanakali Hospital, Erbil, [3]Department of Medicine, College of Medicine, University of Duhok, [6]Department of Hematology, Azadi Hospital, Duhok, Kurdistan Region, Iraq

Address for correspondence:
Dr. Bryar Sabah Rashid, Department of Hematology, Hiwa Cancer hospital, Sulaymaniyah, Kurdistan Region, Iraq.
E-mail: bryarsabah@gmail.com

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Abstract:

BACKGROUND: The clinical course of patients with chronic lymphocytic leukemia (CLL) is heterogeneous. Certain patients go through a brisk illness progression, and others stay alive for quite a long time without requiring treatment.

OBJECTIVE: This study was conducted to evaluate the impact of clinical staging, age, gender, and treatment initiation on the survival of CLL patients in Kurdistan-Iraq.

MATERIALS AND METHODS: A total of 239 CLL patients from Oncology Centers from Kurdistan-Iraq were enrolled in a retrospective study from January 1, 2010, to December 31, 2020. A standardized questionnaire was used to obtain demographics data, presenting features, blood investigations, and imaging results. The diagnosis and treatment assessment was based on the International Workshop of CLL, and clinical staging was performed using both Rai and Binet classifications. There were two groups of patients (watch and wait) and (treated) groups.

RESULTS: The median age at the diagnosis was 64 years old with a male: female ratio of 2.3:1. Eighty-three patients (34.7%) were diagnosed incidentally and about one-third of the patients presented with advanced stage, and also, 62.3% of the patients received therapy throughout the study period. The 3-year overall survival was (81.1%) (95% confidence interval 74.3%–87.9%). Of particular interest to report that advanced age, Binet Stage C, and hemoglobin <10 g/dl have adversly impacted the outcome.

CONCLUSION: Despite the study limitations, the resulted CLL outcome approximates the Western countries reported figures.

Keywords:

Binet staging, chronic lymphocytic leukemia, survival, watch and wait

Introduction

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia seen by hematologists. The disease incidence increases significantly with age,[1,2] reaching 30 cases per 100,000 annually at age over 80 years with associated male predominance.[3,4] CLL in Western countries

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is 10–20 times higher than in Asia, suggesting that genetic factors, environmental factors, or both affect vulnerability to the disease.[5] The disease pathology accumulates monoclonal, mature, CD5+ B-cells in the peripheral blood, bone marrow, and secondary lymphoid organs.[6]

The diagnostic criteria according to the 2018 international workshop of CLL (IwCLL) update: absolute count of clonal B-lymphocytes in the peripheral blood (5×10^9/L), sustained for at least 3 months, with a predominant population of morphologically mature-appearing small lymphocytes.[7]

The clinical course of CLL is enormously heterogeneous, and the value of the two commonly used staging systems in CLL [Table 1] lies in their prognostic implications for survival.[8]

CLL standard management approach is careful observation, irrespective of risk factors, unless patients meet the IWCLL criteria for "active disease" that requires treatment.[9]

When the patients have at least 1 of the following criteria should be treated:

1. Evidence of progressive marrow failure
2. Massive or progressive or symptomatic splenomegaly
3. Massive lymph nodes or progressive or symptomatic lymphadenopathy (LAP)
4. Progressive lymphocytosis with an increase of ≥50% over 2 months or lymphocyte doubling time <6 months
5. Autoimmune complications, including anemia or thrombocytopenia that are not responding to corticosteroids
6. Symptomatic or functional extranodal involvement (e.g., skin, kidney, lung, and spine)
7. Disease-related symptoms as defined by any of the following: [10]
   a. Unintentional weight loss of ≥10% within the previous 6 months
   b. Significant fatigue (i.e., ECOG performance scale two or worse; cannot work or unable to perform usual activities)
   c. Fevers ≥38.0°C for two or more weeks without evidence of infection
   d. Night sweats for ≥1 month without evidence of infection.

The iwCLL guidelines make a detailed description of the evaluation of the treatment response.[4] Moreover, the timing of response assessment for therapies with a definite treatment duration (such as chemoimmunotherapeutic approaches) must be at least 2 months after finishing therapy.[10]

The current study was initiated to evaluate the impact of clinical staging, age, and gender on treatment response and survival of CLL patients in Kurdistan region of Iraq.

Materials and Methods

Study design and patients

This retrospective cohort study encompassed 239 patients with *de novo* CLL from Kurdistan region of Iraq (including Nanakali Hospital-Erbil 117 patients, Hiwa Hospital-Sulaymaniyah 100 patients and Azadi Hospital-Duhok Cancer centres 22 patients) throughout the period from January 1, 2010, to December 31, 2020.

The enrolled cases were diagnosed according to the International Workshop of CLL (IwCLL). Clinical staging was performed using both Rai and Binet classifications. The patients were then divided into two groups: those who only needed observation (watch and wait) and those who had one or more indications for treatments according to IwCLL criteria for active disease.[10]

Clinical assessment

All medical files of the patients were reevaluated. A standardized comprehensive questionnaire was used to obtain detailed information regarding demographics data, age, gender, family history of CLL, presenting clinical features, and blood investigations (complete blood count, blood film, Coomb's test, and flow cytometry). Furthermore, imaging studies results, including (ultrasound of the neck, axilla, inguinal, and abdomen) were also recorded. Finally, the treatment regimens used and their responses were documented too.

Concerning treatment responses, according to IwCLL response criteria assessed by the senior clinical

Table 1: Rai classification and Binet staging systems for chronic lymphocytic leukaemia

System	Clinical features	Median survival (years)
Rai stage (simplified 3-stage)		
0 (low risk)	Lymphocytosis in blood and marrow only	>10
I and II (intermediate risk)	Lymphadenopathy, splenomegaly +/− hepatomegaly	7
III and IV (high risk)	Anaemia, thrombocytopenia	0.75-4
Binet group		
A	Fewer than three areas of lymphadenopathy; no anaemia or thrombocytopenia	12
B	More than three involved node areas; no anaemia or thrombocytopenia	7
C	Haemoglobin <100 g/L platelets <100×10 g/L	2-4

hematologists.[10] In this study, the overall response rate (ORR) was used to evaluate the therapy's response.

Ethical consideration

The ethical committee approved the study at Kurdistan Board of Medical Specialization. All methods were performed per the Helsinki Declaration, and verbal informed consent was obtained from all enrollees and documented within the laboratory database.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) software version 24 (SPSS Inc, Chicago, IL, USA). Descriptive statistics were presented as median and range, and Bar charts were used to demonstrate some variables diagrammatically. For studying the survival curve, the Kaplan–Meier survival curve was used, and the Log-rank test was used to study the significance between different survival curves. P =0.05 was used as a cutoff point for the significance of statistical tests.

Results

The distribution of 239 *de novo* CLL cases among different age categories is shown in Figure 1. The median patients' age at the diagnosis was 64 years old (range 35–92 years), and the majority of cases were aggregated in >60 years' age categories. Younger patients (<40 years) and over 80 years' patients formed a minor population. Moreover, 166 patients (69.5%) were male, and 73 (30.5%) were female (male: female ratio of 2.3:1), and male predominance was reported in all age groups.

At presentation, 83 patients (34.7%) were diagnosed incidentally during the routine examination, while in contrast, 156 (65.3%) patients were symptomatic. LAP and splenomegaly were the most common presenting features, seen in 57.6% and 51.1% of patients, respectively, whereas hepatomegaly was reported in 15.3% of patients [Table 2].

Anemia (Hb ≤10 g/dl) was evident in 22.8% of CLL patients at diagnosis and thrombocytopenia in 24.2%.

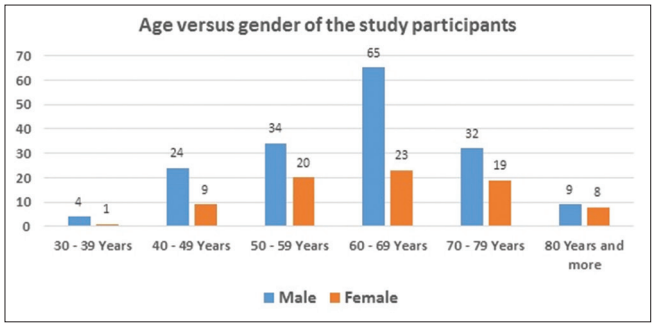

Figure 1: The distribution of age and gender among chronic lymphocytic leukaemia patients

Further, CD38-positive CLL accounted for 15.3% of the enrolled cases. About clinical staging, (32.6%) patients presented with advanced Rai Stages (III and IV) and (28.3%) patients presented with Stage C Binet staging system [Table 3].

In the current cohort, 136 patients (57%) had received chemotherapy from the start (advanced disease) including fludarabine, cyclophosphamide, and rituximab (FCR) in 45 (33.1%) patients, (bendamustine and rituximab) BR in 30 (22.2%) patients, both FCR + BR in 10 (7.3%) patients also chlorambucil alone or in combination in 21 (15.4%) patients, while for the rest 30 (22%) patients other protocols were applied. On other hand, 103 (43%) patients didn't receive any kind of chemotherapy (early disease), of them 13 (12.6%) had required the installation of chemotherapy after around 24 months from the disease onset. More, an ORR to FCR protocol and BR protocol was reported as (89.6%) and (90%), respectively. Furthermore, the three most common indications for treatment in the current study were increasing anemia or thrombocytopenia in (36%) of the patients, bulky or progressive LAP, or splenomegaly in (27.2%), and

Table 2: Demographic, clinical and haemogram parameters

Variable	Category	Percentage
Age (years)	>65	39.1
	≤65	60.9
Sex	Male	69.5
	Female	30.5
Splenomegaly	Yes	51.1
	No	48.9
Hepatomegaly	Yes	15.25
	No	84.5
Lymphadenopathy	Yes	57.6
	No	42.4
Flow cytometry CD38	Positive	15.3
	Negative	84.7
Haemoglobin level (mg/dl)	≤10	22.8
	>10	77.2
Platelet level	≥100,000	75.8
	<100,000	24.2
Treatment plan	Watch and wait	63.5
	Treatment given	36.4

Table 3: Rai and Binet staging

Staging	Category	Percentage
Rai	0	24.3
	I	13.0
	II	30.1
	III	10.0
	IV	22.6
Binet	A	46.4
	B	25.3
	C	28.3

B-symptoms in (26%). Furthermore, 96 patients (38.4%) had two or more indications for treatment.

Survival

The 3-year overall survival of CLL patients in the current study was (81.1%)(95% confidence interval 74.3%–87.9%). Kaplan–Meir survival study has demonstrated that advanced-stage disease manifested by stage Binet C and anemia has been linked to poor outcome, *P* value was 0.006 and 0.001, respectively. Similarly, advanced age > 65 years has shown to be considerably associated with an inferior outcome (*P* = 0.001) [Figure 2]. While on the other hand, gender, advanced Rai stage, and therapy did not offer a superior survival to CLL patients in this research (*P* = 0.56, 0.48, and 0.20), respectively. At the end of the current study, 83.82% of the patients were alive and 16.18% died.

Discussion

The current cohort has included 239 *de novo* CLL patients, aged between 35 and 92 years old representing the largest cohort of patients reported from Iraq addressing CLL patients' outcomes in relevance to demographic and clinicolaboratory parameters. The median age of CLL patients in this study (64 years) is comparable to previously reported regional figures from Baghdad/Iraq; Al-allawi *et al* and Al-kasab *et al*.[11,12] (60 years) and from Erbil/Kurdistan-Iraq (65 years),[13] and two other figures from Turkey (65),[14] Iran (63),[15] and some Western countries.[2,7] Furthermore, this work had confirmed male predominance among CLL patients in various age categories in accordance with previous studies.[2,13,14]

Reports from developed countries revealed that most CLL cases are diagnosed based on routine blood investigations in asymptomatic participants.[16,17] In contrast, only (34.7%) of our patients were diagnosed incidentally, whereas 65.3% were symptomatic at presentation, which might be attributed to a variation in the biology of the disease.[18,19] Having said that, less than one-fourth of the cases had presented with anemia and/or thrombocytopenia, and reflected by over two-thirds of the enrolled cases presented with early-stage disease, and eventually a superior outcome. With a 3-year OS of 81.1%, the current study's overall outcome is comparable to earlier published studies from developed Western countries[20-22] while higher than reports from nearby countries, Turkey 36.5% and Iran 64%.[23,24] In addition, our figure is more favorable than

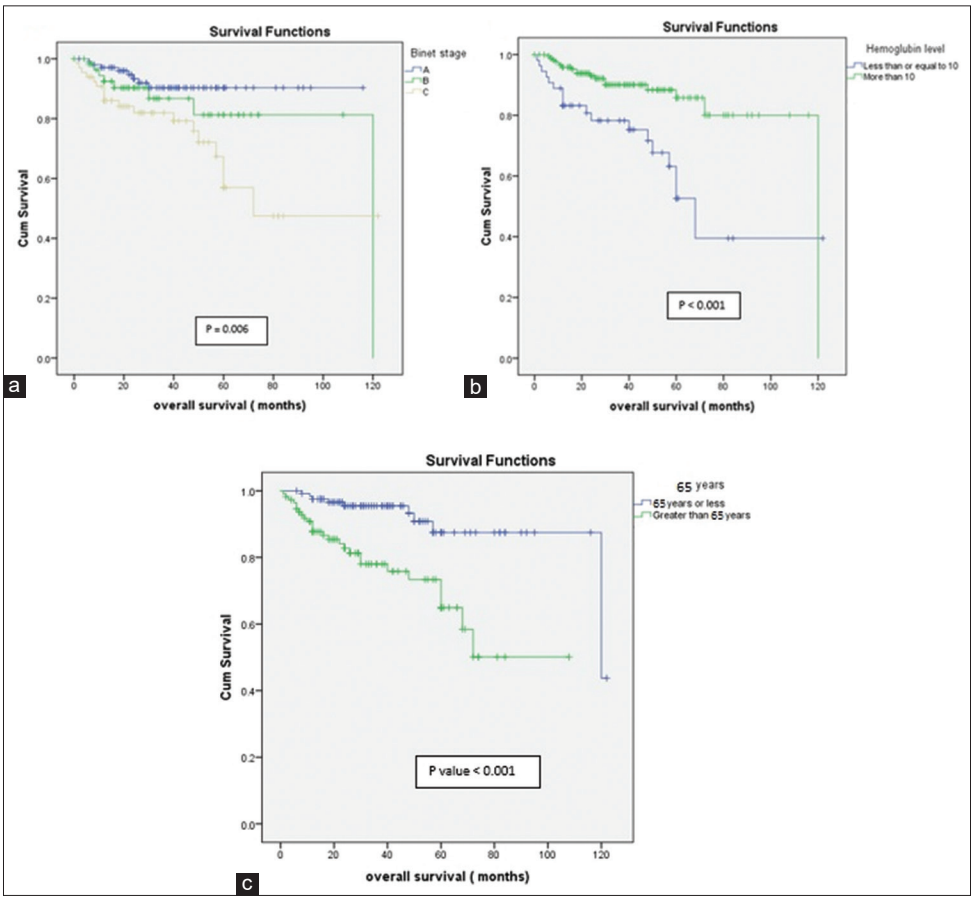

Figure 2: Survival of chronic lymphocytic leukaemia patients according to (a) Binet stage, (b) Haemoglobin, (c) Age

two earlier Iraqi studies, which showed a 5-year OS of 50%[12] and 67.9%, respectively.[13] These differences might be attributed to the improved health care services, including a better patient referral system and the availability of immunophenotyping facilities that have offered an early diagnosis of asymptomatic cases referred to oncology centers, as well as adherence and compliance with standardized therapy protocols. In general, in this study, our patients' clinical and hematological features were similar to those reported in previous studies.[13,18,25,26]

Age has been repeatedly shown to be an independent predictor of survival in CLL patients.[7] in accordance with previous studies, this study has demonstrated that advanced age >65 years has been associated with an inferior outcome in elderly CLL patients.[2,27] On the other hand, females did not reveal a more favorable clinical course than males contradicting some earlier studies.[28,29]

Further, Binet Stage C patients and anemia have negatively impacted the patients' outcome in agreement with others,[2,8] unlike advanced Rai stage that did not predict a worse outcome in accordance with some other studies.[2,30]

The proportion of CLL patients in this study who had recieved therapy is higher than previous western figures[31,32] and this might be explained by the lack of consistent indications for CLL treament among various hospitals and hematologists in Kurdistan-Iraq where anemia or thrombocytoepnia might has been considered as an indication for CLL therapy prior the exclusion of autoimmune causes which are not uncommon in CLL, also the nonspecific symptoms in patients' history misinterpreted as disease related symptoms. Moreover, the most prevalent indications for initiating therapy (increasing anaemia or thrombocytopenia) for the enrolled CLL patients were also shared with other researches.[4,5]

Finally, the currently reported ORR for FCR and BR is in concordance with Western countries' results.,[5,33-35] although we have to admit that the patients' number in this category is low to consider the response rates as representative figures. Other limitations of the current study are the lack of minimal residual disease monitoring and cytogenetic studies at enrollment or follow-up. However, such restrictions are shared by other studies from developing countries with limited resources or expertise.

Conclusion

The current work has demonstrated that our patients' clinicohematological characteristics are comparable to previous regional and international data. Despite some limitations, the resulting outcome approximates the Western countries' reported figures. Moreover, the need to further improve CLL cases' outcome remains prudent in our country as it is throughout the world. Finally, larger cohorts are recommended to predict CLL patients survival by correlating with molecular genetic studies.

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Conflicts of interest
There are no conflicts of interest.

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