ZANCO Journal of Pure and Applied Sciences
The official scientific journal of Salahaddin University-Erbil
https://zancojournals.su.edu.krd/index.php/JPAS

ISSN (print):2218-0230**, ISSN (online):** 2412-3986**, DOI: http://dx.doi.org/10.21271/zjpas**

RESEARCH PAPER

Co-Morbidities and Treatment Decisions in Newly Diagnosed CLL Patients Cross All Disease Stages in Kurdistan Region-Iraq

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Article History:
Received: 30/06/2021
Accepted: 28/07/2021
Published: 20/12 /2021

A B S T R A C T:

Background: Chronic lymphocytic leukemia (CLL) is one of the most common leukemias in Iraq as in other areas of the world, but with younger age involvement in comparison with western population. As in all hematological malignancies, risk stratification of patients with CLL is an essential step in treatment planning.

Aim of study: To evaluate the daily life activity and co-morbidity effects on choosing appropriate lines of treatment for the best interest of CLL patients according to cumulative illness rating scale index (CIRS).

Patients & Methods: A cross sectional review study conducted in three hematology- oncology health care facilities in Kurdistan region – Iraq, (Nanakaly hospital - Erbil, Hiwa hospital in Sulaimani and Azadi hematology oncology center in Duhok) throughout the duration of three years period starting from 1st of January, 2018 till 31st of December, 2020 using a sample of 250 patients diagnosed to have CLL. The CIRS index was applied by the researchers through measuring its score for 14 body systems and calculating the final cumulative index score for each patient.

Results: In the current study, 159 CLL patients (63.6%) in Kurdistan region were treated, while 91 of them (36.4%) were treatment naïve. There was a highly significant association between advanced Rai staging of CLL patients and treatment provision ($p<0.001$). A highly significant association was observed with Binet stage C and among patient treatment group ($p<0.001$). No significant differences were observed between treatment and non-treatment groups of CLL patients regarding total CIRS index score ($p=0.06$). In the present study, 52 (20.8%) of the treated patients were dead, in comparison to 19.25 (7.7%) of the treatment naïve ones.

Conclusions: The staging and risk stratification of CLL patients is an important initial step in planning their management. Treatment planning of CLL patients in Kurdistan region depends on either Rai and/or Binet staging, but the CIRS was not widely applied previously for further in-depth stratification and disease management.

KEY WORDS: Chemotherapy, Chronic lymphocytic leukemia, CIRS index.
DOI: http://dx.doi.org/10.21271/ZJPAS.33.6.1
ZJPAS (2021) , 33(6);1-11 .

1.INTRODUCTION :

Chronic lymphocytic leukemia (CLL) is the most frequent type of leukemia among Western population with incidence of 3.79 per 100,000 population[1, 2]. Despite the indolent nature of CLL and its rather good prognosis, CLL might have an unpredicted course and outcomes with resistance to standard management regimens in many cases and despite recent advances in CLL treatment however, the disease is still regarded as a malignant condition that is associated with shorter life expectancy in comparison to healthy peoples[3]. Chronic Lymphocytic Leukemia, is categorized into two subsets that are different by clinical presentations. These are recognized through the detection of the un-mutated or mutated immunoglobulin heavy-chain variable region gene (*IGHV*), which indicates the origin of staging for normal B cell differentiation [4].

As stated above, CLL commonly affects older aged population[5, 6]. Most of these patients are also affected by other medical conditions[7], more specifically other cancers, these co-morbidities become the main obstacle in either choosing or continuing CLL treatment protocols or become the actual cause of death in the future[8]. Additionally, accumulated evidence and experience showed that survival duration of patients with cancer shortens with increased frequency of co-morbidities [9]. However, the burden of these co-morbidities on the outcome of CLL is still exactly unknown. Many authors evaluated the role of co-morbidities in changing both survival duration or mortality rate [10-12] and intolerance to treatment or resistance [13, 14]. Despite that, only few researches enrolled a population data [11, 12] however they did not put the real cause of death in their consideration.

In spite of wide variations in the course of CLL which has been obvious in last year's, however, more clinical concern was directed toward patients with high-risk. High risk CLL patients were defined depending on poor outcome of CLL through; (1) recognizing CLL patients with progressive disease, refractory to treatment or short response duration with poor prognosis; (2) predictive role for poor prognosis at diagnosis and (3) recognizing co-morbidities, organ dysfunction and lack of general physical activity that could be an obstacle for continuing the treatment and worsen the prognosis of CLL. Patients with advanced risk need further monitoring and care than those with lower risk and this risk stratification is essential in management of CLL [15].

Although CLL patients can clinically present with a variety of symptoms, however, the vast majority of them are asymptomatic and the diagnosis of CLL is mostly incidentally made on doing a complete blood picture and flowcytometry.

In order to classify CLL into specific prognostic groups (high or low risk groups), two clinical staging systems were introduced and widely applied [16, 17]. The CLL Rai staging system is widely used in the United States, while the Binet staging is widely practiced in Europe. These staging systems successfully detect the significance of marrow function and specify the advanced risk or late stages of CLL commonly depending on presence of either anemia or thrombocytopenia or both [4].

The performance status of CLL patients especially among the elderly aged ones is very important in the assessment of co-morbidities and physical fitness before planning treatment. Co-morbidities are common among CLL patients and unfortunately many oncologists seem not to pay enough attention to the patient co-morbidities during treatment planning despite its negative impact on the prognosis and outcome. Many different measurement tools can be selected to assess the physical fitness of CLL patients. One of the most common tools in use is the Cumulative Illness Rating Scale (CIRS) which measure 14 body systems and is graded by a five-point (0 – 4) pathophysiological severity scale to assess co-morbidities in the body organ systems [18]. Many resources from previous literature revealed that the CIRS is a valid predictor for physical fitness in CLL patients and helpful in planning for management. The CIRS is including both illness severity and co-morbidity in equal component that makes it a useful tool in the prediction of future outcomes. Moreover, the CIRS analyzes each item separately, which is a criterion that made it useful also in analyzing the real cause of death, hospitalization and disability [19-21].

Although, CLL is less frequent type of leukemia in Iraq including Kurdistan region [22], however about half the cases in Kurdistan region usually present at an advanced stage at time of diagnosis[23]. Unfortunately, the management plan for CLL in Iraq is still depending on classical staging systems neglecting the role of co-morbidities and physical fitness of patients [24, 25]. For all of these reasons we conduct this study which aimed at evaluating the daily life activity (DLA) and co-morbidity effects on choosing appropriate lines of treatment for the best interest of the patients according to the CIRS index.

Patients and Methods

This is a cross sectional review study conducted in three hematology- oncology health care facilities in Kurdistan region – Iraq. (Nanakaly hospital in Erbil, Hiwa hospital in Sulaimani and Azadi hematology – Oncology center in Duhok) throughout the duration of three years period from 1st of January, 2018 to 31st of December, 2020. The study participants were all cases of chronic lymphocytic leukemia, (CLL) patients admitted to one of the three above mentioned hematology oncology centers. All newly diagnosed treatment naïve CLL Patients who were diagnosed at, and/or referred to any of the three hematology-oncology centers during the study period were included in this study. Patients with missed data and the presence of other hematological malignancy were excluded. The ethical considerations were implemented according the Helsinki declaration. while the ethical approval of health authorities was granted from Kurdistan Board Ethical Committee and Confidentiality of data. Hence the confidentiality of patients' info data was respected and protected throughout the study period. After eligibility to inclusion and exclusion criteria, a total number of 250 CLL patients were selected and enrolled in this study.

Data were collected by the researchers from saved records of CLL patients in the three facilities of Kurdistan region, patients and/or their family members were contacted and requested data were collected directly and via filling a well-designed prepared questionnaire, which included both demographic and clinical characteristics of the study patients, (age, gender, centers of care, race, occupation and body mass index), patients staging (Binet stage, Rai staging and Cumulative Illness Rating Scale for advanced stage whichever applied) treatment indication and outcome, survival duration and current status (if still a life). Diagnosis of CLL was done according to the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) [20].

According to the age, patients were distributed into five age groups ranged from 25 years to 94 years. Binet and/or Rai CLL staging systems were used according to medical ~~findings~~ and investigations findings (physical examination and investigation (Lymphadenopathy and hepatomegaly, splenomegaly in addition to complete blood picture for lymphocytosis, anemia, thrombocytopenia, and immune-phenotyping). The survival duration patient outcomes and follow up was reported and assessed accordingly throughout the duration of the study.

Data were collected and statistically analyzed by Statistical Package of Social Sciences (SPSS) software version 22. Chi square and Fischer's exact tests were applied for analyzing the data as

suitable. Kaplan-Meier curve was used to assess the survival duration of the patients. Level of significance (p value) was regarded statistically significant if it was 0.05 or less.

Results

This study included a total of 250 treatment naïve CLL patients whom visited one of the three Kurdistan hematology – oncology centers at the time of diagnosis (Suliamani: 122 (48.8%, Erbil:103 (41.2%) and Duhok: 25 (10%). Their Age Ranged Between:
(35 - 92, Mean 63. St.D 11.85). Gender wise:170 (68%) of them were males and the remaining 80 (32%) were females. Depending on either Ria or Binet staging systems, treatment was received by 159 (63.6%) of them, while 91 (36.4%) of them were untreated and hence they were divided into two groups. (A: treatment group and B: non-treatment group). No significant statistical differences were observed between both groups regarding: age (p=0.6), gender (p=0.06), centers of treatment (p=0.4), race (p=0.6), occupation (p=0.2) and BMI (p=0.1). (**Table 1**).

No significant differences were observed between both groups regarding the time from symptoms & signs appearance until time of diagnosis (p=0.5). There was a highly significant association between advanced, high risk Rai staging of CLL patients and treatment receival, while low risk Rai staging was significantly associated with the treatment naïve group. (p<0.001). Similarly, a highly significant association was observed with Binet stage C among patients in the treatment group (p<0.001). a weak though statistically non-significant difference were observed between the treatment and non-treatment groups regarding total CIRS index score (p=0.06). No significant differences were observed between treated and non-treated patients regarding survival (p=0.2). There was a significant relationship between treatment and outcome of patients (p=0.007), although 33 out of 159 patients (20.8%) of the treatment group 7 out of 91 (7.7%) of non-treatment group were already dead at the time of data collection. (***Table 2***).

Table 1: Distribution of CLL patients demographic characteristics

Variable	**All CLL patients**				**P**
	Treated		**Not treated**		
	No.	**%**	**No.**	**%**	
Age					0.6 ^{NS}
<50 years	27	17.0	11	12.1	
50-59 years	35	22.0	19	20.9	
60-69 years	52	32.7	37	40.7	
70-79 years	32	20.1	19	20.9	
≥80 years	13	8.2	5	5.5	
Gender					0.09 ^{NS}
Male	114	71.7	56	61.5	
Female	45	28.3	35	38.5	
Centers					0.4 ^{NS}
Sulaimani	80	50.3	42	46.2	
Hawler	61	38.4	42	46.2	
Duhok	18	11.3	7	7.7	
Race					0.6 ^{NS}
Kurdish	144	90.6	84	92.3	

Arabic	15	9.4	7	7.7	
Occupation					0.2 NS
Housewife	38	23.9	30	33.0	
Public servant	15	9.4	14	15.4	
Self employed	42	26.4	19	20.9	
Retired	41	25.8	19	20.9	
Unemployed	23	14.5	9	9.9	
Body mass index					0.1 NS
Normal	69	43.4	37	40.7	
Overweight	67	42.1	47	51.6	
Obese	23	14.5	7	7.7	
Total	**159**	**63.6**	**91**	**36.4**	

S=Significant, NS=Not significant.

Table 2: Distribution of total CLL patients' staging, survival and outcome according to treatment status

Variable	**All CLL patients**				**P**
	Treated		**Not treated**		
	No.	**%**	**No.**	**%**	
Time from symptoms & signs to diagnosis					0.5 NS
≤1 month	111	69.8	60	65.9	
>1 month	48	30.2	31	34.1	
Rai staging					**<0.001** S
Stage 0	20	12.6	42	46.2	
Stage I	20	12.6	12	13.2	
Stage II	45	28.3	32	35.2	
Stage III	23	14.5	1	1.1	
Stage IV	51	32.1	4	4.4	
Binet stage					**<0.001** S
Stage A	47	29.6	71	78.0	
Stage B	51	32.1	15	16.5	
Stage C	61	38.4	5	5.5	
Total CIRS score					0.06 NS
<6	121	76.1	80	87.9	
7-12	36	22.6	11	12.1	
>12	2	1.3	0	-	
Advanced stage					**<0.001** S
Yes	74	46.5	5	5.5	
No	85	53.5	86	94.5	
Indicated for treatment					**<0.001** S

No	0	-	90	98.9	
Yes	159	100.0	1	1.1	
Survival					0.2 NS
<60 months	125	78.6	77	84.6	
≥60 months	34	21.4	14	15.4	
Outcome					**0.007** S
Alive	126	79.2	84	92.3	
Dead	33	20.75	7	7.69	
Total	**159**	**63.6**	**91**	**36.4**	

S=Significant, NS=Not significant.

No significant differences were observed between treated advanced stage CLL patients and not treated advanced stage CLL patients regarding age (p=0.5), gender (p=0.6), centers (p=0.5), race (p=0.4), occupation (p=0.2) and BMI (p=0.1). (**Table3**)

Table 3: Distribution of advanced stage CLL patients' general characteristics according to treatment status.

Variable	**Advanced stage**				**P**
	Treated		**Not treated**		
	No.	**%**	**No.**	**%**	
Age					0.5 NS
<50 years	17	23.0	0	-	
50-59 years	14	18.9	1	20.0	
60-69 years	24	32.4	2	40.0	
70-79 years	12	16.2	2	40.0	
≥80 years	7	9.5	0	-	
Gender					0.6 NS
Male	51	68.9	3	60.0	
Female	23	31.1	2	40.0	
Centers					0.5 NS
Sulaimani	47	63.5	3	60.0	
Hawler	17	23.0	2	40.0	
Duhok	10	13.5	0	-	
Race					0.4 NS
Kurdish	67	90.5	5	100.0	
Arabic	7	9.5	0	-	
Occupation					0.2 NS
Housewife	19	25.7	2	40.0	
Public servant	3	4.1	1	20.0	
Self employed	16	21.6	2	40.0	

Retired	27	36.5	0	-	
Unemployed	9	12.2	0	-	
Body mass index					0.1 NS
Normal	36	48.6	1	20.0	
Overweight	26	35.1	4	80.0	
Obese	12	16.2	0	-	
Total advanced stage Pt. patients	**74**	**93.6**	**5**	**6.4**	

S=Significant, NS=Not significant. Pt. = Patients .

No significant differences were observed between advanced stage patients in both groups regarding: Time from symptoms & signs to diagnosis (p=0.7), Total CIRS score (p=0.7), Survival (p=0.2) and Outcome (p=0.1). A highly significant concordance was observed between indication for and actual treatment receival in advanced stage patients (p<0.001). (**Table 4)**

Table 4: Distribution of advanced stage CLL patients' Staging, Survival and Outcome according to treatment Status.

Variable	**Advanced stage**				**P**
	Treated		**Not treated**		
	No.	**%**	**No.**	**%**	
Time from symptoms & signs to diagnosis					0.7 NS
≤1 month	55	74.3	4	80.0	
>1 month	19	25.7	1	20.0	
Total CIRS score					0.7 NS
<6	48	64.9	4	80.0	
7-12	24	32.4	1	20.0	
>12	2	2.7	0	-	
Indicated for treatment					**<0.001** S
No	0	-	5	100.0	
Yes	74	100.0	0	-	
Survival					0.2 NS
<60 months	59	79.7	5	100.0	
≥60 months	15	20.3	0	-	
Outcome					0.1 NS
Alive	53	71.6	5	100.0	
Dead	21	28.4	0	-	
Total	**74**	**93.6**	**5**	**6.4**	

S=Significant, NS=Not significant.

The mean survival of all CLL patients was 39.4 months (median=33 months), the mean survival of treated CLL patients was 42.7 months (median=39 months), while the mean survival of non-treated CLL patients was 34.2 months (median=29 months). (**Figure 1**)

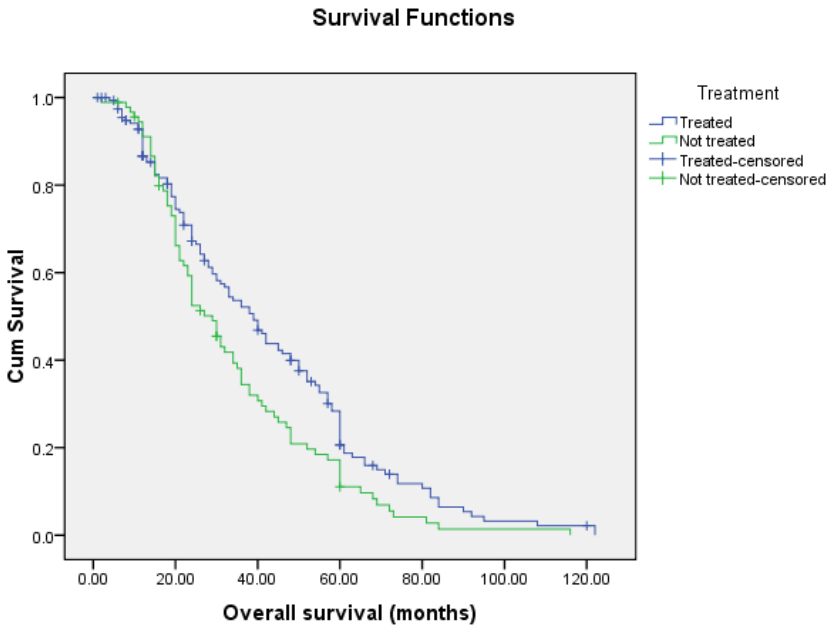

Figure 1: Kaplan-Meier curve of all CLL patients (blue=treated), (green=not treated).

The overall mean survival of advanced CLL patients was 42.7 months (median=40 months), mean survival of treated advanced stage CLL was 44.1 months (median=40 months), while the mean survival of non-treated advanced stage CLL patients was 25 months (median=21 months). (**Figure 2**)

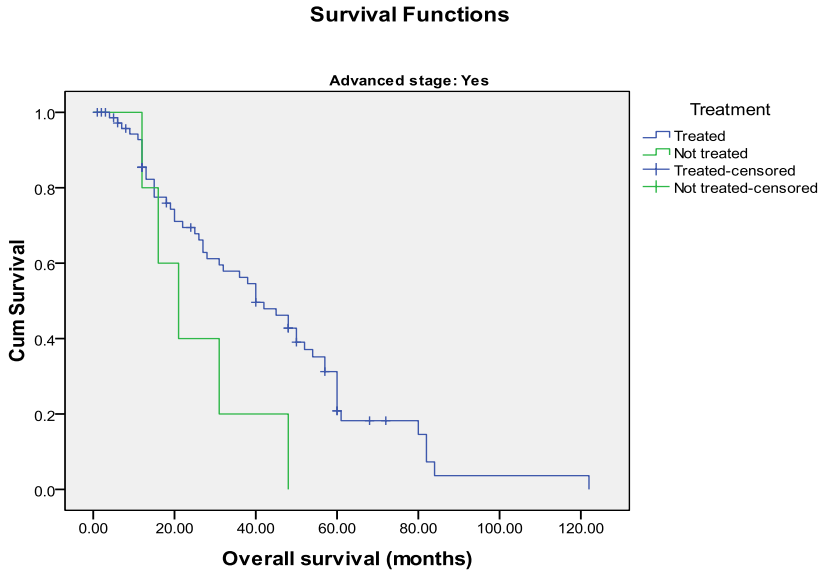

Figure 2: Kaplan-Meier curve of advanced stage CLL patients (blue=treated), (green=not treated).

Discussion

Chronic lymphocytic leukemia is well known to have variable prognosis, as some CLL patients might be totally asymptomatic and present with no significant pathology and do not need any treatment apart from a (watchful waiting) approach, while others might need urgent treatment [27]. There are many clinical and demographic parameters which might be considered in choosing both the time and the type of treatment initiation for CLL patients [28].

The current study showed that 159 (63.6%) of CLL patients in Kurdistan region were ~~treated~~ on treatment, while 91 (36.4%) of them were not. In

contrary to a study done by Hasan K.M in Erbil city-Kurdistan region which showed that only 16.2% of CLL patients were treated [23.] , This study showed a higher number of treated cases. This difference might be due to a number of reasons like differences in inclusion criteria and a bigger sample size as it included CLL patients from three Kurdistan cities in addition to differences in the patients' demographic characteristics and economic status. Similar though less obvious results were found when this study findings were compared to the results of Pamuk et al [29] study in Turkey which revealed that only 48% of CLL patients received treatment while 52% of them didn't.

In this study a highly significant association between advanced stage disease, indication for and actual treatment receival. ($p<0.001$). Treatment decision of CLL patients is dependable on many factors such as age of patients, physical fitness [30], co-morbidities [31], in addition to factors affecting the treatment of relapsed CLL like increased age, severe adverse events of CLL treatment and the long duration nature of CLL disease [32]. In Iraq, the CLL disease incidence tend to affect a younger aged patients as compared to other countries [33].

A highly significant association between advanced Rai staging of CLL patients and treatment commencement, while lower risk Rai staging was associated with no treatment ($p<0.001$). This finding is consistent with many studies such as Rai and Jain study in USA [34] and Hallek study in Germany [35] which stated that the Rai staging of CLL patients is useful in prediction for CLL prognosis and helpful for physicians in treatment decision. In general, a high proportion of CLL patients whom participated in this study were at low risk Rai staging. This finding is in concordance to the results of Alawadi study in Iraq [36]. The current study also showed a highly significant association between Binet stage C CLL patients and treatment commencement ($p<0.001$). Letestu et al [37] study in France similarly reported that the implementation of Binet staging system is essential in detection of CLL patients at advanced risk and is important in the treatment planning of CLL patients. A previous study in Germany stated that the decision of CLL treatment is commonly related to Binet stage C; presence of an active disease that is accompanied with progressive lymphadenopathy or organomegaly; associated with physical inability; presence of intolerable symptoms; or rapidly deteriorating hematology investigations measures [38]. The current study also showed a highly significant association between CLL patients with lower risk stage and not to treat decision ($p<0.001$). five advanced stage patients despite having a real and clinically wise indication, however, they refused taking any treatment. These findings are in agreement with results of Flowers et al [39] study in USA which documented that risk stratification is essential in treatment planning of CLL. A highly significant association between CLL patients indicated for treatment and actual treatment receival was revealed ($p<0.001$). Physicians responsible for treating CLL patients should be careful in taking treatment decisions and selecting the best treatment options for those CLL patients indicated for treatment [40]. As shown in the present study, the treatment decision of CLL in Kurdistan mainly depends on Rai and/or Binet staging systems taking in consideration other characteristics like presence of active disease or co-morbidities or severe symptoms in addition to refusal of advanced age patients for the treatment.

In the current study, a weak but statistically non-significant differences were observed between treatment and not treatment CLL patient groups regarding total CIRS score ($p=0.06$). This finding seems to be in consistence with the results of many studies like Goede et al [10] study in Germany and Satram-Hoang et al [41] study in USA which encouraged the application of CIRS index in risk stratification and treatment plan for CLL patients specifically among elderly age patients. Unfortunately however and due to delay in updating the national management guidelines for the diagnosis and management of CLL patients in Iraq and Kurdistan region the implementation of this useful tool might have resulted in the negligence of the effects of co-morbidities and physical ability on treatment decision especially in elderly patients despite the fact that the proportion of elderly age CLL patients in our country is less than other Western countries.

Regarding death as a final sequelae, the current study found that, 33 patients (20.75%) of the treatment group, and 7 (7.69%) non-treatment group died as an overall outcome. This finding is inconsistent with results of Mjali et al study in Iraq[33,] which revealed that 11.9% of treated CLL patients were died. The high proportion of death in treated CLL patients might be attributed to advanced stage of CLL disease, elderly age and presence of other co-morbidities. In USA, a study conducted by Weide et al [42] on 724 CLL patients followed from 1995 to 2017, revealed that 43% of them were died, with CLL being the cause of the

death in only 36% of their patients, while 26% of them died due to other co-morbidities. The overall mean survival of CLL patients in the current study was (39.4 months). This mean survival is close to results of Payandeh et al [43] study in Iran which reported mean overall survival of CLL patients as (38.5 months). Although no significant differences in survival between treated and untreated CLL patients in all patients or in advanced stage CLL patients, the survival of treated advanced stage CLL patients was longer than the survival of untreated advanced stage CLL patients. This finding is similar to results of der Straten et al [44] study in Netherlands which stated that the survival of advanced stage CLL patients mostly depends on better treatment and close follow up.

The present study concluded that the staging and risk stratification of chronic lymphocytic leukemia is important in its management. The treatment planning of CLL patients in Kurdistan region primarily depends on Rai and/or Binet staging systems, but the Cumulative Illness Rating Scale (CIRS) is still not perfectly implemented in Iraq and specifically in Kurdistan, hence this study highly recommends the customization and implementation of the (CIRS) tool in all hematology – oncology centers for taking the co-morbidities and physical fitness into consideration in CLL treatment planning.

Acknowledgments

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

Conflict of interest

Declared none.

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