

Outcome of treatment among chronic lymphocytic leukemia and its correlation to Rai staging system in Kurdistan region of Iraq

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ABSTRACT

Background: Chronic lymphocytic leukemia is common adulthood leukemia with low incidence in Kurdistan region of Iraq. Staging of chronic lymphocytic leukemia is essential in treatment planning and the pattern of response is variable.

Aim of study: To evaluate the Rai staging distribution of patients with chronic lymphocytic leukemia in Kurdistan region/Iraq and its correlation with the treatment outcome.

Patients & Methods: A retrospective cross sectional review study conducted in three Hemato/oncology centers in Kurdistan for duration of eleven years through the period from 1st of January, 2010 to 31st of December, 2020 on convenient sample of 170 chronic lymphocytic leukemia patients. Diagnosis of chronic lymphocytic leukemia was done according to the International Workshop on Chronic Lymphocytic Leukemia. The Rai staging was done by the clinical hematologist in Hemato/oncology center according to clinical evaluation and laboratory investigations. The pattern of the treatment response was determined according to the International Workshop on Chronic Lymphocytic Leukemia (iwCLL)

Results: The Rai staging of our patients was 0 in 15.3% of them, stage I in 12.4%, stage II 30%, stage III 13.5% and stage IV 28.8%. The treatment response of studied sample was complete response (43.5%), partial response (17.6%), stable (14.1%), no response (21.8%) and progressive (2.9%). A highly significant association was observed between no response to treatment and advanced Rai staging and also a highly significant association was observed between death outcome of patients and advanced Rai staging.

Conclusions: The treatment response of patients with chronic lymphocytic leukemia is directly related to Rai staging as patients with advanced Rai staging had lower treatment response rate.

Keywords: Chronic Lymphocytic Leukemia, Rai staging, Treatment response.

مخرجات العلاج لدى مرضى سرطان الدم الليمفاوي المزمن في ارتباط مع نظام تصنيف الراي في اقليم كردستان - العراق

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الخلاصة

الخلفية: ابيضاض الدم الليمفاوي المزمن هو من الامراض السرطانية الشائعة عند البالغين ولكن نسبة حدوثه اقل شيوعا من اقليم كردستان العراق . يعتبر تقسيم المرض الى مراحل ضروريا عند بدء العلاج وكذلك مدى الاستجابة للعلاج .

هدف الدراسة : لمعرفة توزيع راي التدريجي للمرضى المصابين بسرطان الدم الليمفاوى المزمن فى إقليم كردستان / العراق وتقييم العلاقة مع نتيجة العلاج.

المرضى والطرق : دراسة مراجعة مقطعية بأثر رجعى أجريت فى ثلاثة مراكز للأورام فى كردستان لمدة ١١ عامًا خلال الفترة من ١ يناير ٢٠١٠ إلى ٣١ ديسمبر ٢٠٢٠ على عينة ملائمة من ١٧٠ مريضًا بسرطان الدم الليمفاوى المزمن. تم تشخيص سرطان الدم الليمفاوى المزمن وفقاً لورشة العمل الدولية حول سرطان الدم الليمفاوى المزمن. تم إجراء تصوير الرأى بواسطة كبير الأطباء فى مركز الأورام وفقاً للتحقيقات الطبية. تم تحديد نمط الاستجابة العلاجية وفقاً لورشة العمل الدولية حول سرطان الدم الليمفاوى المزمن (iWCLL)

النتائج : كان تصنيف الرأى لمرضانا صفرًا فى ١٥.٣٪ منهم ، والمرحلة الأولى فى ١٢.٤٪ ، والمرحلة الثانية ٣٠٪ ، والمرحلة الثالثة ١٣.٥٪ والمرحلة الرابعة ٢٨.٨٪. كانت الاستجابة العلاجية للعينة المدروسة استجابة كاملة (٤٣.٥٪) ، استجابة جزئية (١٧.٦٪) ، مستقرة (١٤.١٪) ، عدم استجابة (٢١.٨٪) وتقدمية (٢.٩٪). لوحظ وجود ارتباط مهم للغاية بين عدم الاستجابة للعلاج والتدرج المتقدم للرأى ، كما لوحظ وجود ارتباط مهم للغاية بين نتيجة وفاة المرضى وتدرج الرأى المتقدم.

الاستنتاجات : الاستجابة العلاجية للمرضى المصابين بابيضاض الدم الليمفاوى المزمن مرتبطة ارتباطاً مباشراً بتدرج الرأى حيث أن المرضى الذين يعانون من مراحل متقدمة من الرأى لديهم معدل استجابة أقل للعلاج.

الكلمات المفتاحية : سرطان الدم الليمفاوى المزمن ، نظام تصنيف راي ، نمط الاستجابة للعلاج .

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is the commonest adulthood leukemia in western countries affecting older age population¹. However, the incidence of CLL is low in Asia especially in Middle East countries². The CLL is slightly prevalent in male gender population³. Till now, exact etiology of CLL is obscure, with role of genes and environment as predisposing factors. Genetic theory in pathogenesis of CLL is superimposed by low CLL incidence in East countries and positive family history of some CLL patients⁴. Although the CLL is known as a naïve B-cell lymphocytes neoplasm, there is a role for post-germinal center⁵.

Patients with chronic lymphocytic leukemia mainly asymptomatic at diagnosis, but if symptomatic, the symptoms of CLL are variable and presented with unclear symptoms of general weakness or fatigue⁶. Generally, at time of CLL diagnosis, most patients are well. At diagnosis, the lymphadenopathy is recorded in most of patients, splenomegaly is observed in about half of patients, while the hepatomegaly is less incident^{7,8}. In some rare CLL cases and with disease progression, the patients presented with accidental reduction of weight, fever and night sweats (B symptoms)⁹. The blood picture of CLL patients manifested mainly by lymphocytosis, in addition to anemia and thrombocytopenia (15-30% of cases)^{7,8}. The cornerstone in CLL diagnosis is explored by peripheral blood immunophenotyping through increased CD5⁺/CD23⁺ monoclonal B lymphocytes level in Peripheral Blood in duration of more than 3 months¹⁰.

The Rai and Binet clinical staging of CLL were firstly used at seventies of last Century and still

utilized till now. These staging systems are easily applied clinically as they are dependable on clinical data taking in consideration anemia, thrombocytopenia, liver, spleen and lymph nodes involvement. Despite that, some CLL cases at Rai stages 0 and 1 or Binet stage A showed rapidly progressive disease, whilst the other CLL cases reported stability of disease status in several years^{7,8}. The Rai staging is classified into five groups (0, I, II, III and IV) and Binet stages are grouped into three categories (A, B and C). Many literatures evaluated the role of many risk factors affecting prognosis of CLL other than clinical and biological prognostic factors like male gender, higher white blood cell count, increase in lymphocyte in short duration, abnormal bone marrow histopathology¹¹ with increased beta-2 microglobulin, lactate dehydrogenase and other markers like CD23 and thymidine in addition to prognostic markers detected by flow cytometry such as CD38 and ZAP-70 protein¹². In spite of prognostic role of these markers, the clinical staging has higher sensitivity in detecting the burden of CLL and in prediction of CLL disease progression⁹. In addition to the role of the state of the mutation of mutated immunoglobulin heavy chain variable region (IGHV), 17p deletion and TP53 mutation is important before initiation of therapy, they are expensive and requires delicate technical efforts which limits its application routinely in clinical practice¹³.

Treatment of CLL is designed according clinical staging and specific guidelines¹⁴. CLL patients at early stage (Rai stage 0, Binet stage A) require no treatment and accompanied with long survival^{7,8}. CLL patients at intermediate stage (Rai stage I or II, Binet stage B) are treated if accompanied with

disease activity signs and have median survival of eight years, while CLL patients at advanced stage (Rai stage III or IV, Binet stage C) must have treatment and characterized by short survival. Nowadays, the CLL survival becomes longer as new effective drugs have been introduced^{15,16}.

The CLL is long duration incurable disease. For that, it requires long duration follow up and observation. The treatment response of CLL should be done at least two months after completing the recommended therapy by physical examination and evaluating the bone marrow. Treatment response is dependable firstly on major symptoms and burden of tumor (lymph nodes, liver and/or spleen size, constitutional symptoms and lymphocyte count) and secondly on hematopoietic system (platelets count, hemoglobin and bone marrow findings). Treatment response is classified into complete remission (CR), partial remission (PR), stable disease (SD) and progressive disease (PD)¹⁵.

The aim of present study is to evaluate the Rai staging distribution of patients with chronic lymphocytic leukemia in Kurdistan region/Iraq and its correlation with the treatment outcome.

PATIENTS AND METHODS

This study was a retrospective cross sectional review study conducted in three Hemato/oncology centers in three cities of Kurdistan region (Hiwa Cancer Hospital, Nanakali Hospital, Duhok Hematology Center). The duration of the study was eleven years through the period from 1st of January, 2010 to 31st of December, 2020. All patients with a diagnosis of CLL whom have been diagnosed at, and/or referred to regional hematology-oncology centers during study duration were the study population. The inclusion criteria included patients with CLL from all age groups, diagnosed by flow cytometry (BD FACSCanto™ II flow Cytometry) or bone marrow biopsy with *immunohistochemistry* who completed treatment. Small lymphocytic leukemia (SLL), Monoclonal B cell lymphocytosis of < 5000 monoclonal lymphocytes / mm³, Richter's syndrome, B-cell prolymphocytic leukemia, Hairy-cell leukemia, disease duration of less than one year, patients were not treated, patients refused treatment, missed data and the leukemic phase of indolent NHL (follicular, splenic marginal zone, mantle cell lymphoma) were excluded from the study. The ethical considerations were implemented according Helsinki Declaration regarding ethical approval of Health authorities, an ethical approval was taken from Kurdistan Board Ethical Committee and confidentiality of data. A convenient sample of 170 chronic lymphocytic

leukemia patients was selected after eligibility to inclusion and exclusion criteria.

The data were collected by the researcher from saved records of patients in three Hemato/oncology centers and some information were collected directly from patients and fulfilling a prepared questionnaire. The questionnaire was designed by the researcher and the supervisor. The questionnaire included the followings: general characteristics of CLL patients (age, gender, residence, Binet stage and Rai staging) treatment characteristics (treatment type and treatment cycles) and outcome (Treatment response, current status and survival duration). The chemotherapy treatment of studied CLL patients was Chlorambucil, Bendamustine-Rituximab and Ibrutinib and FCR (Fludarabine + Cyclophosphamide + Rituximab). Sixty-three CLL patients were treated by FCR as frontline treatment and 107 CLL patients were treated by other chemotherapies and as followings; 47 patients by Bendamustine-Rituximab, 37 patients by Chlorambucil and 23 patients by Ibrutinib.

The age of CLL patients was categorized into five groups and ranged from 28 years to 88 years. The residence of CLL patients was distributed into three cities of Kurdistan region. The Binet and Rai staging of CLL patients was done by the clinical hematologist in Hemato/oncology center according to medical and investigations findings^{7,8}. Additionally, the Rai staging was grouped into low risk, moderate risk and high risk according to updated Rai staging. The treatment response was assessed by the researcher and supervisor according to iwCLL¹⁴ into five categories (complete response, partial response, stable, no response and progressive). The death and alive outcome was assessed by researcher. The survival duration of CLL patients was reported according to duration of follow up.

The data collected were analyzed statistically by Statistical Package of Social Sciences software version 22. The 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 CLL patients. Level of significance (p value) was regarded statistically significant if it was 0.05 or less.

RESULTS

This study included 170 patients with (CLL) with mean age of (66.4 years) and range of 28-88 years; the majority (72%) of patients were 60 years and above, and only 10% of patients were less than 50 years age. Male CLL patients were more than females (68.8% vs. 31.2%). The residence of CLL patients was Hawler for 45.9% of them, Sulaimani for 37.1% of them and Duhok for 17.1% of them. The Binet stage of our patients was distributed as followings; stage A (33.5%), stage B (30.9%) and stage C (35.9%). Rai staging of our patients was 0 in 15.3% of them, stage I in 12.4%, stage II 30%, stage III 13.5% and stage IV 28.8%. Updated Rai classification included low risk (15.2%), moderate risk (42.4%) and high risk (42.4%). (Table 1)

Table 1: General characteristics of CLL patients.

Variable	No.	%
Age mean±SD (66.4±12.5 years)		
<50 years	17	10.0
50-59 years	30	17.6
60-69 years	57	33.5
70-79 years	34	20.0
≥80 years	32	18.8
Gender		
Male	117	68.8
Female	53	31.2
Residence		
Hawler	78	45.9
Sulaimani	63	37.1
Duhok	29	17.1
Binet stage		
Stage A	57	33.5
Stage B	52	30.6
Stage C	61	35.9
Rai staging		
Stage 0	26	15.3
Stage I	21	12.4
Stage II	51	30.0
Stage III	23	13.5
Stage IV	49	28.8
Updated Rai classification		
Low risk	26	15.2
Moderate risk	72	42.4
High risk	72	42.4
Total	170	100.0

The FCR chemotherapy was the treatment of 37.1% of our patients, while 62.2% of the patients were treated by other chemotherapies. Mean chemotherapy treatment cycles was (5.2 cycles); 63.5% of our recruited patients received 6 cycles and more of chemotherapy treatment. The treatment response of studied sample was complete response (43.5%), partial response (17.6%), stable (14.1%), no response (21.8%) and progressive (2.9%).

The current status of CLL patients was either dead (29.4%), or alive (70.6%) and the mean survival was (35.7 months); the five years overall survival was 21.2%, while 78.8% of patients had survival of less than 5 years. (Table 2)

Table 2: Chemotherapy treatment and outcomes of CLL patients.

Variable	No.	%
Chemotherapy treatment		
FCR	63	37.1
Other	107	62.9
Treatment cycles mean±SD (5.2±2 cycles)		
<6 cycles	62	36.5
≥6 cycles	108	63.5
Treatment response		
Complete response	74	43.5
Partial response	30	17.6
Stable	24	14.1
No response	37	21.8
Progressive	5	2.9
Status		
Dead	50	29.4
Alive	120	70.6
Survival mean±SD (35.7±24.9 months)		
<60months	134	78.8
≥60months	36	21.2
Total	170	100.0

*Other chemotherapies (Chlorambucil, Bendamustine-Rituximab and Ibrutinib)

No significant differences were observed between CLL patients with different Rai staging regarding age ($p=0.1$) and gender ($p=0.6$). There was a significant association between Hawler residents of CLL patients and advanced Rai staging ($p=0.003$). (Table 3)

Table 3: Distribution of CLL patients' general characteristics according to Rai staging.

Variable	Rai staging				P
	0 No. (%)	I No. (%)	II No. (%)	III and IV No. (%)	
Age					0.1 ^{NS}
<50 years	0 (0)	2 (9.5)	4 (7.8)	11 (15.3)	
50-59 years	2 (7.7)	8 (38.1)	8 (15.7)	12 (16.7)	
60-69 years	11 (42.3)	7 (33.3)	17 (33.3)	22 (30.6)	
70-79 years	5 (19.2)	3 (14.3)	10 (19.6)	16 (22.2)	
≥80 years	8 (30.8)	1 (4.8)	12 (23.5)	11 (15.3)	
Gender					0.6 ^{NS}
Male	19 (73.1)	12 (57.1)	35 (68.6)	51 (70.8)	
Female	7 (26.9)	9 (42.9)	16 (31.4)	21 (29.2)	
Residence					0.003 ^S
Hawler	6 (23.1)	6 (28.6)	20 (39.2)	46 (63.9)	
Sulaimani	13 (50.0)	11 (52.4)	23 (45.1)	16 (22.2)	
Duhok	7 (26.9)	4 (19.0)	8 (15.7)	10 (13.9)	

S=Significant, NS=Not significant.

There was a significant association between FCR treatment and studied patients with advanced Rai staging ($p=0.003$). No significant differences were observed between CLL patients with different Rai staging regarding number of treatment cycles ($p=0.6$) and survival ($p=0.9$). A highly significant association was observed between no response to treatment and CLL patients with advanced Rai staging ($p<0.001$) and also a highly significant association was observed between death outcome of patients and advanced Rai staging ($p<0.001$), deaths were mostly CLL related (Table 4)

Table 4: Distribution of CLL treatment characteristics and outcomes according to Rai staging.

Variable	Rai staging				P
	0 No. (%)	I No. (%)	II No. (%)	III and IV No. (%)	
Treatment					0.003 ^S
FCR	4 (15.4)	8 (38.1)	14 (27.5)	37 (51.4)	
Other chemotherapies	22 (84.6)	13 (61.9)	37 (72.5)	35 (48.6)	
Treatment cycles					0.6 ^{NS}
<6 cycles	8 (30.8)	6 (28.6)	21 (41.2)	27 (37.5)	
≥6 cycles	18 (69.2)	15 (71.4)	30 (58.8)	45 (62.5)	
Treatment response					<0.001 ^S
Complete response	15 (57.7)	16 (76.2)	21 (41.2)	22 (30.6)	
Partial response	5 (19.2)	1 (4.8)	14 (27.5)	10 (13.9)	
Stable	5 (19.2)	2 (9.5)	10 (19.6)	7 (9.7)	
No response	1 (3.8)	2 (9.5)	6 (11.8)	28 (38.9)	
Progressive	0 (0)	0 (0)	0 (0)	5 (6.9)	
Status					<0.001 ^S
Dead	2 (7.7)	3 (14.3)	10 (19.6)	35 (48.6)	
Alive	24 (92.3)	18 (85.7)	41 (80.4)	37 (51.4)	
Survival					0.9 ^{NS}
<60months	21 (80.8)	16 (76.2)	39 (76.5)	58 (80.6)	
≥60months	5 (19.2)	58 (23.87)	12 (23.5)	14 (19.4)	

S=Significant, NS=Not significant.

The overall mean survival of all treated CLL patients was 45.1 months (median=40 months), the overall mean survival of CLL patients with stage 0 was 38.2 months (median=39 months), for stage I was 43.3 months (median=41 months), for stage II was 42 months (median=29 months), for stages III and IV was 56.9 months (median=69.5 months). (Figure 1)

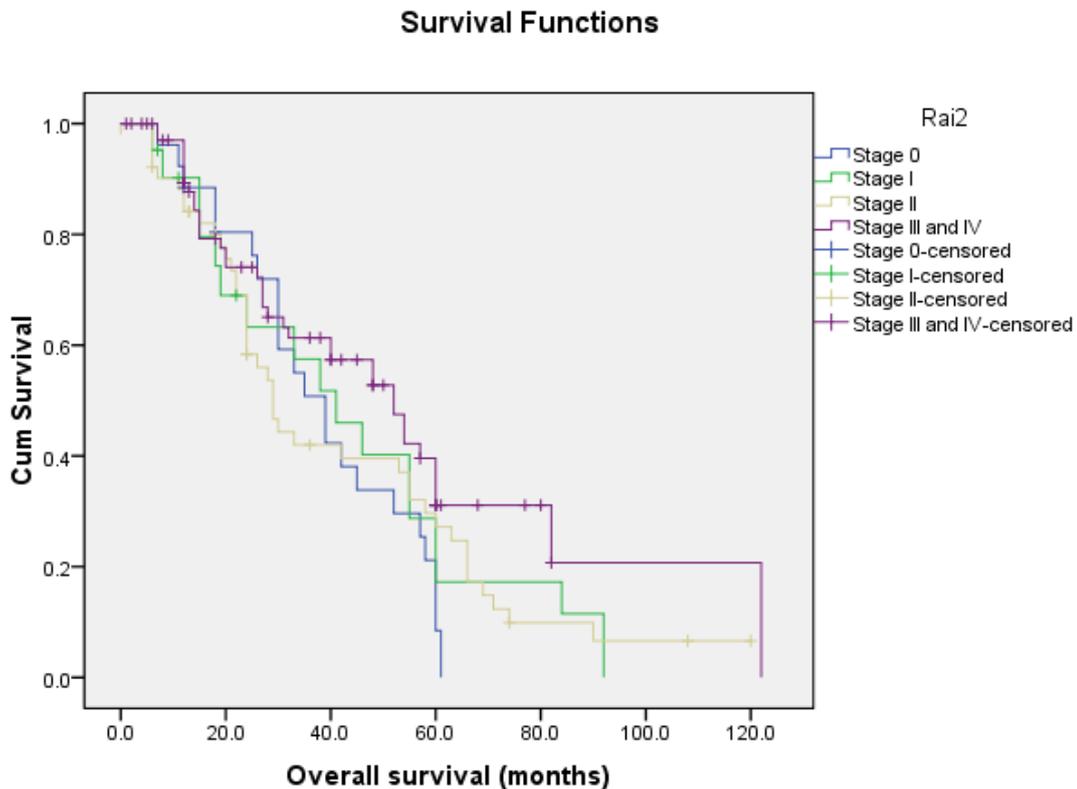


Figure 1: Kaplan-Meier curve of CLL patients according to Rai staging (blue=stage 0), (green=stage I), (brown=stage III), (purple=stage III and IV).

DISCUSSION

The chronic lymphocytic leukemia is the less frequent type of leukemia in Iraq¹⁷, however, about half the CLL cases in Kurdistan region are at advanced risk¹⁸.

In present study, Rai staging of studied patients was 0 in 15.3% of them, stage I in 12.4%, stage II 30%, stage III 13.5% and stage IV 28.8%. These findings are close to results of Hasan retrospective study in Erbil city-Kurdistan on sample of 105 patients with CLL Generally, the prevalence of CLL patients at advanced Rai staging in Kurdistan is higher than other parts of Iraq¹⁸. Present study revealed that treatment response of studied sample was distributed as followings; complete response (43.5%), partial response (17.6%), stable (14.1%), no response (21.8%) and progressive (2.9%). These findings are better than results of Najji study in Iraq¹⁹ on sample of 49 CLL patients in Baghdad teaching hospital enrolled mostly with intermediate to advanced Rai staging and reported

treatment response of 12.5% complete response, 65% partial response and 22.5% no response. This difference may be due to better diagnostic and treatment facilities of Kurdistan Hemato/oncology center than other Iraqi Hemato/oncology centers. Our study findings regarding treatment response are close to results of Meunier et al²⁰ -retrospective study in France which found that overall response rate of CLL patients treated by chlorambucil, bendamustine and rituximab was (66.2%) with complete remission of (31.8%). The differences in treatment response of CLL are mainly related to treatment regimens used²¹.

The current study showed a highly significant association between no response to treatment and CLL patients with advanced Rai staging ($p < 0.001$). This finding is consistent with results of many literatures such as Rai and Jain study in USA²², Moreno et al²³ study in Spain and de Faria et al²⁴ study in Brazil which all documented that treatment response of CLL patients is directly linked to Rai

staging of them at diagnosis. Generally, CLL patients at Rai 0 must be followed with no indication for treatment disease progression is observed. Many previous studies carried out in Western countries reported that survival of patients with low risk CLL (early stage) was not prolonged after treatment by alkylating agents²⁵⁻²⁸. Dighiero et al²⁵ found that incidence of epithelia cancer was higher among treated CLL patients at low risk in comparison to untreated CLL patients at low risk. Our study found also highly significant association was observed between death outcome of patients and advanced Rai staging ($p < 0.001$). This finding coincides with results of Velez et al²⁹ study in USA which stated that advanced Rai staging (stages III and IV) of patients with chronic lymphocytic leukemia were significantly had higher mortality rates and high risk of other cancers like skin cancer. In Spain, a study conducted by Villavicencio et al³⁰ revealed a significant association between Rai staging and Charlson comorbidity index of patients with CLL and patients with advanced Rai staging were more prone for comorbidities and higher death rates. However, our study showed no significant relationship between survival of CLL patients and Rai staging. This finding is inconsistent with results of Faria et al²⁴ study in Brazil which reported a significant association between advanced Rai staging of patients with CLL and shorter survival. This inconsistency might be due to difference in health infrastructure and discrepancy in diagnostic techniques between Hemato/oncology centers of different countries.

Our study also showed variations in survival of studied patients according to Rai staging; however, the overall mean survival of all treated CLL patients was 45.1 month. This finding is lower than results of Hasan study in Erbil city-Kurdistan which reported over all mean survival of (60 months)¹⁸. This difference might be attributed to difference in inclusion criteria between two studies as our study included treated CLL patients only.

In present study, there was a significant association between FCR treatment and studied patients with advanced Rai staging ($p = 0.003$). This finding is similar to results of Herling et al³¹ study in UK which documented that early FCR treatment for patients with low risk CLL is not useful in changing the outcome and survival of patients, while it is effective in patients with high risk (advanced Rai staging). Our study also showed a significant association between Hawler residents of CLL patients and advanced Rai staging ($p = 0.003$). This fact might be due to fact that Hawler city is the Capital of Kurdistan region that made it the recipient of all referred advanced Rai staging CLL

cases from other Hemato/oncology centers in other cities.

In conclusion, the treatment response of patients with chronic lymphocytic leukemia is directly related to Rai staging as patients with advanced Rai staging had lower treatment response rate. The Rai staging is an optimal guideline for treatment regimen selection and final outcome of patients with CLL. Our study urged the Oncologist to adopt the clinical staging systems as the basic steps in treatment planning and prognosis for chronic lymphocytic leukemia.

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Conflict Of Interest

Declared none.

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