RESEARCH PAPER

The Correlation of initial hematological feature with advanced stage in Chronic Lymphocytic Leukemia in Kurdistan Region of Iraq

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Background and objective: Chronic lymphocytic leukemia (CLL) is considered by an accumulation of matured lymphocytes in the blood, bone marrow, spleen. And lymph .We aimed to find the correlation of initial hematological feature with advanced stage in CLL. **Methods:** A retrospective study was conducted on 138 patients with CLL, confirmed by flow cytometry of peripheral blood collected in Hiwa Hematological and Oncological Hospital in Sulaimani, Nanakaly Hospital in Hawler, and Azadi Hematology - Oncology Center in Duhok, Kurdistan Region of Iraq dated from January 1, 2010, to December 31, 2020. **Results:** The mean age of 63.07±11 years with male predominance. The majority of patients at presentation were Rai Stage II and Binet stage A. The frequency of DAT positivity was found in (6.5%), which also established appositive relationship with advanced stage, there were statistically significant relation of hemoglobin level, platelet counts, LDH level to Rai stage and Binet stage disease (P value <0.001), No association were noted between different age groups and initial laboratory finding, also no relation of gender to staging. **Conclusion:** In the present study there was a significant relation between laboratory findings (hemoglobin, platelet count, LDH levels) to with staging, in addition DAT positivity demonstrated a significant correlation with advanced stage, those with High LDH levels associated with more advanced Rai stage.

1.INTRODUCTION :

Chronic lymphocytic leukemia (CLL) is considered by the accretion of matured-lymphocytes in the peripheral blood, bone marrow, spleen, and lymph nodes(Yun, Zhang and Wang, 2020). The diagnosis of CLL needs the presence of ≥5 × 109/L B lymphocytes in the peripheral blood, continued for at least 3 months with clonality confirmed by flow cytometry according to International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria(Hallek *et al.*, 2018)Also express CD19, CD5, and CD23 with weak or no expression of surface immunoglobulin (Ig), CD20, CD79b, and FMC7, CLL is the furthermost common leukemia of adults in the west nations, Most CLL patients in the over-all population are elderly (median age 71.5 years)(Yun, Zhang and Wang, 2020).

The clinical presentation at diagnosis is very variable. About 60% of patients are asymptomatic, and the disease may be doubted after a routine complete blood count. While symptomatic, patients present with unclear symptoms of fatigue or weakness(Mercer, 2002). Patients generally have a good performance status at diagnosis, Lymphadenopathy with cervical and axillary lymph nodes bilaterally and symmetrically being affected, Splenomegaly is generally mild to moderate and is observed in nearly 50% of cases; hepatomegaly is less common, and rare at diagnosis, when the disease progresses, patients can have B symptoms (Rodrigues *et al.*, 2016).

Some of the chronic lymphocytic leukemia patients can presented with cytopenia's. These contain autoimmune hemolytic anemia, immune thrombocytopenic purpura, pure red cell aplasia and autoimmune agranulocytosis. Between CLL associated cytopenia's, autoimmune hemolytic anemia(AIHA) is the greatest common and considered by a positive direct antiglobulin test(DAT), known as Direct Coombs test with elevated serum bilirubin, increased reticulocytes and presence of spherocytosis on peripheral blood film examination (Haider *et al.*, 2019). AIHA is generally detected in advanced stages of disease and associated with poor prognostic group, DAT status at the time of disease appearance shows new prognostic indicator for overall survival (Abbas *et al.*, 2015).

Assessment of such patients should include a complete blood count with differential; flow cytometry of the peripheral blood to define the immunophenotype of circulating lymphocytes; and check of the peripheral smear, however Assessment of the bone marrow is not usually required, but should be examined in those patients with unexplained cytopenia's (Kanti RR, Stilgenbauer S and Aster JC, 2019).

The serological test in CLL, is standard and consist of Lymphocyte doubling time (LDT), serum beta2-microglobulin (s-β2M), serum thymidine kinase (s-TK) and lactic dehydrogenase (LDH) are the greatest common straight serum markers in CLL and expect poor results. LDT ≤ 12 months expects poor prognosis while LDT > 12 months associates with an extended treatment-free period and survive. LDH is an pointer of time to first treatment (TTFT) and related with shorter PFS, overall survival (OS) and Richter's transformation It is still of prognostic value in patients with trisomy 12 (Rosenquist *et al.*,

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2013).it is commonly understood as reflecting high tumor burden or tumor aggressiveness and conveys a poor prognosis in CLL(Sagatys and Zhang, 2012).

The Rai and Binet clinical staging systems are useful to stratify patients, describing their risk and prognosis. (Hallek *et al.*, 2018).

Administration protocol for treatment of CLL consist of combination of immunotherapy and standard chemotherapy for patients with symptomatic, advanced or progressive disease. While for patients with stable disease the "watch and wait" algorithm is usually deployed (Hallek *et al.*, 2018),(Madu *et al.*, 2019) .

2. Materials and Methods:
2.1. Study design and patients

The present study was a retrospective observational study that involved 138 patients who had CLL were enrolled. The patients were admitted to Hiwa Hematological and Oncological Hospital in Sulaimani, Nanakaly Hospital in Hawler, and Azadi Hematology Oncology Center in Duhok, Kurdistan Region Iraq, from January 1, 2010, to December 31, 2020.

Patients involved in this study were established according to the International workshop on chronic lymphocytic leukemia (IWCLL)(Hallek *et al.*, 2018).

> The inclusion criteria included all patients who had been diagnosed with CLL, (both gender male and female, age more than 35 years, newly diagnosis, and all races.)
> Exclusion criteria all patients with
> 1-Incomplete data
> 2-Age younger than 35 years
> 3-Transforamtion of cases during data collection,
> 4-Small Lymphocytic Lymphoma
> 5- Hairy Cells Leukemia and others B-Cells Lymphoma.
> The documented data about the patients was collected from the electronic databases of the mentioned hospitals, the demographic features containing (age, gender, race, residency, occupation, BMI.) , presenting features(anemia, fatigue, B-symptoms, lump), hematological panel (complete blood count, blood film, coombs test, retic count, blood group) ,

biochemical panel(lactate dehydrogenase), organomegaly ,peripheral lymphadenopathy confirmed with ultrasound and flow cytometry of peripheral blood was used to confirm the diagnosis but molecular and cytogenetic studies were not done as it was not available

Then we classified our patients according to Rai and Binet staging system (Hallek *et al.*, 2018). Also the patients were treated, followed up and assessed their response according to International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria(Hallek *et al.*, 2018), some patients with a symptomatic early stage disease(Rai 0, Binet A) monitored without therapy, but patients with intermediate –risk and high-risk disease generally received treatment with chemo-immunotherapy and targeting therapy, and assessment of their response at least 2 months after completion of therapy.

2.2. Statistical analysis:

After data collection and prior to data entry and analysis, the questions of study were coded. Data entry performed via using an excel spreadsheet then the statistical analysis was performed by SPSS program, version 21 (IBM SPSS Statistical Package for the Social Sciences). The data presented in tabular forms showing the frequency and relative frequency distribution of different variables. Chi-square test used to compare different qualitative (categorical) variables of the study (to find their association) as comparing different laboratory finding with age groups, sex and the two types of staging (Benit and Modified Rai). Different types of Bar charts and Pie charts as well as arithmetic scale line graphs were used to describe some variables of the study diagrammatically.

2.3. Ethical consideration:

Research Ethical Committee of the Kurdistan Board of Medical Specialties (KBMS) and Cancer Center accepted the study proposal

3. Results

This study comprised 138 patients with CLL, the mean age of 63.07±11, 29 cases are female and 71 patients are male (ranged from 35 to ≥80 years). The major age group was in 50-64 years with 42.8 %. And male: female ratio is 2.45:1, as shown in (Table 1)

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The majority of patients at presentation were Rai Stage II (44 cases, 31.9%), Binet stage A (58 cases, 42.0%) while minimum number of them had Rai Stage III (13 cases, 9.4%), Binet stage B (33 cases, 23.9%) as shown mentioned (Table 2).

The direct anti-globin test positivity was set up in (9 cases, 6.5%), negativity (129 cases 93%). LDH was measured in all patients, it was normal in 52.9 %(n=73) and in 47.1 %(n=65) was above the normal, the others hematological markers are shown in (Table 3).

The relation between different age groups and initial laboratory finding is statistically not significant (P >0.05) as shown in (Table 4).

Regarding the relation of the same age grouping to the staging systems of CLL, It was obvious that there was a highly significant correlation between age and Rai stage of presentation, with majority of patients of Stage II (P value 0.04), but correlation of age with Binet stage and modified Rai staging of presentation are also statistically not significant (P value> 0.05) as shown in table (Table 5)

Regarding the relationship of laboratory finding to the staging of presentation, there are statistically a significant relation of hemoglobin level, platelet counts ,LDH level to Rai stage and Binet stage disease (P value <0.001), but relation of lymphocyte groups, coombs test ,Blood groups of patients to Rai stage and Binet stage are statistically not significant(P value > 0.05) (Table 6).

We also want to discovery any relation between gender of patients and CLL staging systems in (Table 7), we found that more female patients have Rai Stage 0 and Binet stage A disease, while more male patients have Rai Stage II and Binet stage A disease, and both male and female have Modified intermediate risk, but again this relation is also statistically not significant (P value> 0.05).

Table (1): Age distribution of chronic lymphocytic leukemia in KRI

Age	Frequency	Percent
35 - 49 Years	22	15.9%
50 - 64 years	59	42.8%
65 - 79 years	47	34.1%
≥ 80 years	10	7.2%
Total	138	100.0%

Table (2): Staging systems of chronic lymphocytic leukemia patients:

Staging	category	Frequency	Percentage
Rai	0	30	21.7%
	I	15	10.9%
	II	44	31.9%
	III	13	9.4%
	IV	36	26.1%
Binet	A	58	42.0 %
	B	33	23.9 %
	C	47	34.1 %
Modified Rai	Low risk	30	21.7%
	Intermediate risk	59	42.8%
	High risk	49	35.5%

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Table (3): Initial laboratory finding of CLL patients

Laboratory test	Frequency	Percentage
Hemoglobin		
≤ 10	31	22.5%
> 10	107	77.5%
Platelet level		
≥ 100	104	75.4%
< 100	34	24.6%
Lymphocyte groups		
5 – 10	81	58.7%
10.1 – 50	36	26.1%
> 50	21	15.2%
LDH		
Normal Normal (≤ 280 U/L)		52.9%
High (> 280 U/L)	65	47.1%
Coomb's test		
Positive	9	6.5%
Negative	129	93.5%
Blood group		
A + ve	28	29.8 %
B + ve	23	24.5 %
B - ve	1	1.1 %
AB + ve	5	5.3 %
AB - ve	1	1.1 %
O + ve	33	35.1 %
O – ve	3	3.2 %

Tabale (4): Relation between age distribution of CLL patients and initial laboratory finding

Laboratory test	35 - 49 Y	50 - 64 Y	65 – 79 Y	≥ 80 Y	Total	P value
Hemoglobin						
≤ 10	4	12	11	4	31	0.54
> 10	18	47	36	6	107	
Platelet level						
≥ 100	15	43	39	7	104	0.49
< 100	7	16	8	3	34	
Lymphocyte groups						
5 – 10	13	30	31	7	81	0.75
10.1 – 50	6	19	9	2	36	
> 50	3	10	7	1	21	
LDH						
Low (< 140 U / L)	7	22	16	5	50	0.93

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Normal (140 - 280 U/L)	3	10	8	2	23	
High (> 280 U/L)	12	27	23	3	65	
Coomb's test						
Positive	1	4	2	2	9	0.32
Negative	21	55	45	8	129	
Blood group						
A+	3	13	9	3	28	0.78
B+	4	9	8	2	23	
B-	0	1	0	0	1	
AB+	1	1	3	0	5	
AB-	0	0	1	0	1	
O+	5	16	10	4	33	
O-	2	1	0	0	3	

Table (5): correlation between age distributions of CLL patients with staging systems

Staging	35 - 49 Y	50 - 64 Y	65 – 79 Y	≥ 80 Y	Total	P value
Rai staging						
0	1	11	15	3	30	0.04
I	6	8	1	0	15	
II	5	19	18	2	44	
III	2	4	5	2	13	
IV	8	17	8	3	36	
Binet staging						
A	9	24	21	4	58	0.52
B	3	15	14	1	33	
C	10	20	12	5	47	
Modified Rai staging						
Low risk	1	11	15	3	30	0.15
Intermediate risk	11	27	19	2	59	
High risk	10	21	13	5	49	

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Table (6): correlation between laboratory findings of CLL patients with staging systems

Modified Rai staging

Lab. Finding / Rai Staging	Modified Rai staging			Total	P value
	Low risk	Intermediate risk	High risk		
Hemoglobin					
≤ 10	0 (0%)	0 (0%)	31 (100%)	31 (100%)	< 0.001
> 10	30 (28.0%)	59 (55.1%)	18 (16.8%)	107 (100%)	
Platelet level					
≥ 100	30 (28.8%)	59 (56.7%)	15 (14.5%)	104 (100%)	< 0.001
< 100	0 (0%)	0 (0%)	34 (100%)	34 (100%)	
Lymphocyte groups					
5 – 10	21 (26%)	30 (37%)	30 (37%)	81 (100%)	0.06
10.1 – 50	9 (25%)	18 (50%)	9 (25%)	36 (100%)	
> 50	0 (0%)	11 (52.4%)	10 (47.6%)	21 (100%)	
LDH					
Normal (≤ 280 U/L)	19 (26.0%)	25 (34.2%)	29 (39.7%)	73 (100%)	0.09
High (> 280 U/L)	11 (16.9%)	34 (52.3%)	20 (30.8%	65 (100%)	
Coomb's test					
Positive	2 (22.2%)	2 (22.2%)	5 (55.6%)	9 (100%)	0.36
Negative	28 (21.7%)	57 (44.2%)	44 (34.1%)	129 (100%)	
Blood group					
A+	7 (25%)	12 (42.9%)	9 (32.1%)	28 (100%)	0.70
B+	2 (8.7%)	9 (39.1%)	12 (52.2%)	23 (100%)	
B-	0 (0%)	1 (100%)	0 (0%)	1 (100%)	
AB+	1 (20%)	3 (60%)	1 (20%)	5 (100%)	
AB-	0 (0%)	1 (100%)	0 (0%)	1 (100%)	
O+	8 (24.2%)	15 (45.5%	10 (30.3%)	33 (100%)	
O-	0 (0%)	1 (33.3%)	2 (66.7%)	3 (100%)	

Lab. Finding / Benit Staging	Benit staging			Total	P value
	A	B	C		
Hemoglobin					
≤ 10	0 (0%)	0 (0%)	31 (100%)	31 (100%)	< 0.001
> 10	58 (54.2%)	33 (30.8%)	16 (15.0%)	107 (100%)	
Platelet level					
≥ 100	58 (55.8%)	33 (31.7%)	13 (12.5%)	104 (100%)	< 0.001
< 100	0 (0%)	0 (0%)	34 (100%)	34 (100%)	

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Lymphocyte groups					
5 – 10	35 (43.2%)	18 (22.2%)	28 (34.6%)	81 (100%)	0.16
10.1 – 50	19 (52.8%)	8 (22.2%)	9 (25%)	36 (100%)	
> 50	4 (19%)	7 (33.3%)	10 (47.6%)	21 (100%)	
LDH					
Normal (≤ 280 U/L)	32 (43.8%)	14 (19.2%)	27 (37. 0%)	73 (100%)	< 0.001
High (> 280 U/L)	26 (40%)	19 (29.2%)	20 (30.8%)	65 (100%)	
Coomb's test					
Positive	3 (33.3%)	1 (11.1%)	5 (55.6%)	9 (100%)	0.34
Negative	55 (52.6%)	32 (24.8%)	42 (32.6%)	129 (100%)	
Blood group					
A+	10 (35.7%)	10 (35.7%)	8 (28.6%)	28 (100%)	0.47
B+	6 (26.1%)	6 (26.1%)	11 (47.8%)	23 (100%)	
B-	0 (0%)	1 (100%)	0 (0%)	1 (100%)	
AB+	3 (60%)	1 (20%)	1 (20%)	5 (100%)	
AB-	0 (0%)	1 (100%)	0 (0%)	1 (100%)	
O+	15 (45.5%)	8 (24.2%)	10 (30.3%)	33 (100%)	
O-	1 (33.3%)	0 (0%)	2 (66.7%)	3 (100%)	

Benit staging

Table (7): correlation between gender distributions of patients with staging

Gender/ Staging	Gender		Total	P value
	Male	Female		
Rai staging				
0	18	12	30	0.18
I	9	6	15	
II	33	11	44	
III	8	5	13	
IV	30	6	36	
Benit staging				
A	38	20	58	0.45
B	24	9	33	
C	36	11	47	
Modified RAI staging				
Low risk	18	12	30	0.25

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Intermediate risk	42	17	59	
High risk	38	11	49	
Total	98	40	138	

4. Discussion

CLL is the greatest common form of adult leukemia in the Western countries, through maximum of cases in elders above 50(Basabaeen *et al.*, 2019) .

We retrospectively collected 138 patients, the mean age of presentation was 63.1 years old (ranged from 35 to ≥80 years) which are nearby to the results reported in other Iraq studies(Hasan, 2018), (Al-rubaie and Mohammed, 2018), also comparable to the result described in Iran(Payandeh, Sadeghi and Sadeghi, 2015). while the results show a decade younger than US (Brander *et al.*, 2017), (Pulte *et al.*, 2016). This difference can be qualified to the variance in population structure, residence, genetic tendency, environmental factor, disproportion in lifetime expectation and sample size among Iraq and western countries.

In our study the male to female ratio 2.45:1 which was comparable to that of western countries and other world studies (Brander *et al.*, 2017) (Pulte *et al.*, 2016),(Basabaeen *et al.*, 2019),(Abbas *et al.*, 2015). But it was higher than that described by other Iraqi studies (Al-rubaie and Mohammed, 2018),this may also due to variance in sample size. But in very studies clear finding of male predominance was stable. Which might be linked to genetic bases as revealed by results described by Cantu ES, McGill JR et al (Cantú *et al.*, 2013)

In the current study, most patient presented at Rai stage II (31.9%) or Binet stage A (42%) or modified Rai intermediate risk (42.8%), according to the data from other western world such as in brazil and USA are frequently primary seen in Rai stage II (35.6%), Modified Rai intermediate risk (43.2%) and Rai stage II (37.9%), Binet stage A (42.6%) respectively(Faria *et al.*, 2000) , (Pflug *et al.*, 2014). But according to the data from previous study of Iraq most of patients existing at an advance stage such as Rai stage III or IV (59.1%) Binet stage C (55.2%) (Hasan, 2018), (Naji, 2012). also in Iran greatest patient is realized in advanced stage (38.5%) which are various in present study.(Payandeh, Sadeghi and Sadeghi, 2015) may be due to regular review, services now

available for initial recognition and diagnosis of the disease.

We tried to find any relation among staging and their gender but statistically it was not significant while both male and female mostly have modified Rai intermediate Risk and Binet stage A disease.

In current study in relation of age to staging our study showed that advance stage is more common in age 50-64years which was similar to the preceding study done in Iraq (Naji, 2012).also in USA (Parikh *et al.*, 2014).

Also, male was more frequently affected by the disease than female which is similar to a study done in Iran(Payandeh, Sadeghi and Sadeghi, 2015).

We found that in 138 pateints,44 patient blood group was not done(31.95%),majority of our patients have O-positive blood group(33 cases 35.1%) ; we didn't find any connection between blood group and staging in current study, and this may necessity further researches as we could not find any research about ABO blood grouping in CLL, except one paper speaking about the spreading of ABO blood type in patients with leukemia which displays that in CLL patients majority have blood Group O(Ochoa-garcía *et al.*, 2019).

The occurrence positive DAT in current study was (6.5%), Inadequate studies are available from Asian countries, Before only study showed in Erbil city of Iraq has reported 11% of CLL patients showing DAT positivity and its associated with significant anemia, this outcome was higher to that of our study(Hasan, 2018).Various studies conducted in United State, Spain, England and have re-counted a frequency of positive DAT in 4.5%,4.3% and 7.7% of CLL patients respectively However, the prevalence of DAT positivity in our patients appears to be more than in US, Spain, and less than in England these studies conducted in western world (Kyasa *et al.*, 2003)'(Moreno *et al.*, 2010)'(Ward, 2001) .

In this study on 138 CLL patients at diagnosis, DAT positive result was associated with more advanced stage, less predominant in stage A disease, as it was testified to another study in Iraq,

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Asian and America(Hasan, 2018)'(Abbas *et al.*, 2015)'(Dearden *et al.*, 2008).

In current study we found that LDH has statistically significant relation with staging (p-value<0.001) which was comparable to that reported by Asian, Germany and Italy studies(Li *et al.*, 2017)'(Pflug *et al.*, 2014)'(Autore *et al.*, 2019).

Since LDH is an low-priced and usually performed laboratory parameter, also reflect tumor burden and such disease activity, we found that 73(52.9%) patients displayed levels within normal range, and 65(47.1%) patients exhibited elevated LDH levels, in compare elevated LDH levels to previous study in Iraq and Asian was lower (82.9%, 70%) respectively,(Hasan, 2018)'(Al-rubaie and Mohammed, 2018)'(Mozaheb, NazarAbadi and Aghaee, 2012) but in compare to Germany study in current study the elevated LDH level was more than in Germany study (47.1 %versus 34.8%) (Pflug *et al.*, 2014).

In current study Those with high LDH level showed (52.3%, 30.8%) associated with intermediate and high risk of modified Rai staging respectively and 40% with Binet Stage A, this was an arrangement to conducted study in Italy (Autore *et al.*, 2019).

5. Conclusion:

The median age was similar to that observed in Iraq and Iran. . Male –to-female ratio which was comparable to that of western countries and other world studied with male predominance which was obvious in all studies; however, patients more frequently presented at early stage comparable to the western population. And DAT positivity in our setting appears relatively similar to international studies, also an association of positive DAT was found with advanced stage like regional and western studies. Also there was statistically significant relation between laboratory finding to the staging (including hemoglobin, platelet count and LDH levels) similar to the regional and international studies, those with High LDH levels associated with advanced Rai stage.

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