Zagazig University Medical Journal
www.zumj.journals.ekb.eg
Volume29, Issue2, March 2023(469-478)

Manuscript ID ZUMJ-2108-2310 (R1)

DOI **10.21608/zumj.2021.89473.2310**

ORIGINAL ARTICLE

Lymphoid enhancer binding factor-1 (LEF1): as a prognostic factor in patients with Chronic lymphocytic leukemia

Mervat azab[a], Ahmad baraka[a], Shereen el shorbgy[b], Abdullah Mohammad Abd el-hameed[a]*.

a *Clinical Pathology department, Faculty of Medicine, Zagazig University, Egypt*

b Clinical oncology department, Faculty of Medicine, Zagazig University, Egypt

Corresponding author:

Abdullah Mohammad Abdel-hameed*

E-mail address:
abdullahabdelhameed@yahoo.com

Submit Date 2021-08-06

Revise Date 2021-08-22

Accept Date 2021-08-24

ABSTRACT

Background: Chronic lymphocytic leukemia (CLL) is the most common form of leukemia in the world. CLL involves the abnormal activation of Wingless-type (Wnt) signaling pathway. Lymphoid enhancer-binding factor 1 (LEF1) is a member of the LEF1/T-cell factor (TCF) family of transcription factors. The aim of the current study is to evaluate LEF1 expression in CLL and its impact on risk stratification and response to therapy.

Methods: This study was conducted on 32 patients recently diagnosed as chronic lymphocytic leukemia. Complete blood picture, LDH, bone marrow aspiration, immunophenotyping, cytogenetic analysis and assessment of LEF1 expression by real time PCR were done For all patients.

Results: The prognostic value for LEF1 was evaluated. There was a significant difference between Low LEF1 group and high LEF1 group as regards mortality (P .006); all the patients in low LEF1 group were alive at the end of follow up period, while in high LEF1 group five were alive at the end of follow up period and two died during the study. The overall survival of patient's low LEF1 level was longer than patients with high LEF1 level. Such difference was statistically significant (P=0.005).

Conclusion: Level of expression of LEF1 in CLL patients may be valuable in predicting the survival.

Key words: CLL; LEF1; real-time PCR.

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is a B-cell hematological malignancy characterized by the clonal expansion and accumulation of morphologically mature B-lymphocytes in peripheral blood, bone marrow, and secondary lymphoid tissues [1].Lymphoid enhancer-binding factor 1 (LEF1) is a member of the LEF1/T-cell factor (TCF) family of transcription factors. It is a downstream effector of the Wnt/ β -catenin signaling pathway that has crucial roles in extensive cellular processes in differentiation and proliferation as well as hematopoietic cell growth and fate [2]. A number of studies revealed that the pathogenesis of CLL involves the abnormal activation of Wingless-type (Wnt) signaling pathway [3].During canonical Wnt signaling, LEF1/TCF proteins directly interact with β-catenin to induce expression of target genes, including the cell-cycle regulators cyclin D1 and c-myc.1 [4]. Dysregulation of LEF1 expression may result in a number of diseases, where overactive Wnt signaling drives LEF1/the T-cell factor (TCF) family of transcription factors to transform cells. Increased expression of LEF1 affects normal expression of cell cycle and growth-promoting genes, such as Cyclin D1 and c-MYC and disturbs differentiation in hematopoiesis [5].

LEF1 has a functional role in hematopoiesis as well as a putative prognostic impact on several hematological malignancies; among of is the CLL. Menter et al., (2017) stated that LEF1 has a role in diagnosis of CLL [6].

Overexpression of LEF1 has been reported to be involved in solid cancers and leukemia [7], as ALL [8][9], AML [10] and blastic phase (BP) of chronic myeloid leukemia (CML) [11].

METHODS

This Cohort follow up study was carried out at Clinical Pathology, Medical Oncology department, Zagazig University Hospitals, between September 2017 and April 2019. The study included 32 patients recently diagnosed as chronic lymphocytic leukemia,the patients followed for a median follow-up period of 20 months.

All patients in this study were subjected to full history taking, clinical examination

and Laboratory investigations divided into, Routine investigations included, Complete blood count (sysmex XN 2000, Sysmex Corp, JAPAN), liver, kidney function tests, LDH (roche cobas 8000 system, Germany), Bone marrow aspiration and examination, immunophenotyping by flowcytometry and cytogenetic analysis.

Special investigations included, LEF1 expression by quantitative PCR (qPCR): RNAs were extracted from samples using (easy-RED TM Total RNA Extraction Kit, iNtRON Biotechnology, Inc, Korea.). Reverse transcription reaction was performed with each sample using (High Capacity cDNA Reverse Transcription Kit, Applied Biosystems, Thermo Fisher Scientific USA).

Real time PCR was done on "Stratagene Mx3005P system" (Agilent Technologies, USA). All steps were done according to manufacturer recommendations. Threshold cycle (CT) values were registered for each sample well, and were normalized against the house keeping gene *B actin*. The expression of a target gene to an adequate reference gene (housekeeping gene) was calculated (control subjects needed):

ΔCT (sample) = CT LEF1 gene - CT housekeeping gene

ΔCT (control) = CT LEF1 gene - CT housekeeping gene

Next, the ΔΔCT value for each sample was determined by subtracting the ΔCT value of the control from the ΔCT value of the sample: ΔΔCT = ΔCT (sample) – ΔCT (control).

Finally, the normalized level of LEF1 gene expression was calculated by using the formula 2-ΔΔCT.

STATISTICAL ANALYSIS

All information was gathered, tabulated and analyzed using SPSS version 19. Independent samples Student's t-test was used to compare between two groups of normally distributed variables while Mann Whitney U test was used for non- normally distributed variables. Kruskall Wallis test was used to compare between more than two independent groups of non-normally distributed variables. Percent of categorical variables were compared using Chi-square test or Fisher's exact test when appropriate. Spearman's rank correlation coefficient was calculated the significance level was set at $P < 0.05$.

Ethical approval :The study was approved by "Institutional Review Board" (IRB) committee at Faculty of Medicine, Zagazig University. A written consent was taken from all subjects for ethical consideration. This research was carried out in agreement with the Statement of Helsinki.

RESULTS

The LEF1 level in studied group ranged from 0.001 to 234.8 with a mean of 18.6. Cut-off value for LEF1 at diagnosis for survival analysis: A cutoff >9.84 had an AUC of 0.933 (95% CI, 0.786 to 0.991) with a sensitivity of 100% (95% CI, 15.8 - 100.0%) and a specificity of 86.67% (95% CI, 69.3 - 96.2%), P= <0.0001 table (1), (9) and figure (1). The LEF1 level in low group ranged from 0.001 to 9.25 with a mean of 0.036, while in high group ranged from 9.84 to 234.8 with a mean of 29.04 table (2) and figure (2). There was no significant difference between Low LEF1 group and high LEF1 group as regards gender and age (P >0.05) table (3). There was no significant difference between Low LEF1 group and high LEF1 group as regards performance status (PS), easy fatigue, LN enlargement, splenomegaly, hepatomegaly, left hypochondrial pain, B symptoms and accidental discovery (P >0.05) table (4).There was no significant difference between Low LEF1 group and high LEF1 group as regards TLC, absolute lymphocytic count, lymphocytes %, HB level, PLT count, and LDH (P >0.05) table (5). There was no significant difference between Low LEF1 group and high LEF1 group as regards CD19, CD5, CD20, CD23, CD79b, CD38,17p del, Coombs' Test, HCV and Rai staging (P >0.05) table (6). There was no significant difference between low LEF1 group and high LEF1 group as regards treatment and response to treatment (P > 0.05). However, there was a significant difference between Low LEF1 group and high LEF1 group as regards mortality state (P .006). All the patients in low LEF1 group were alive at the end of follow up period, while in high LEF1 group five were alive at the end of follow up period and two died during the study table (7). The follow up period ranged from 10 to 24 months with a mean of 20.2 months.

Survival analysis: After a median follow-up period of 20 months (range, 10-24 months), 6.3 % of patients died (2/32 patients). The 2-year overall survival rate was 93.8% with a mean of 23.2± 0.5 months (95% CI; 22.2 – 24.2 months); however, the median OS was not reached. The overall survival of patient's low LEF1 level was longer than patients with high LEF1 level. Such difference was statistically significant (P=0.005) figure (3), figure (4) and table (8).

Table 1: LEF Level in studied group

LEF(Fold Change)	No. = 32
Median	0.9
Range	0.001 - 234.8

Mean±SD	18.6±51.9

Table 2: LEF.1 Expression of studied group

	LEF.1 Expression					
	Low LEF-1	No. = 25		High LEF-1	No. = 7	
	Median	Min	Max	Median	Min	Max
LEF- 1	.036	.001	9.25	29.04	9.84	243.8

Table 3: Association between LEF Level in studied group and demographic data

		LEF.1 Expression				
		Low LEF-1		High LEF-1		
		Count	Column N %	Count	Column N %	**P**
Gender	Male	12	48.0%	3	42.9%	**.810**
	Female	**13**	**52.0%**	**4**	**57.1%**	

	LEF.1 Expression						
	Low LEF-1			High LEF-1			P
	Median	Min	Max	Median	Min	Max	
Age	52	34	75	59	44	75	.242

Table 4: Association between LEF Level in studied group and clinical data

		LEF.1 Expression				
		Low LEF-1		**High LEF-1**		**p**
		Count	**Column N %**	**Count**	**Column N %**	
Performance status (PS)	-ve	13	52.0%	4	57.1%	**.810a**
	+ve	12	48.0%	3	42.9%	
Easy fatigue	-ve	8	32.0%	4	57.1%	**.225a**
	+ve	17	68.0%	3	42.9%	
LN enlargement	-ve	4	16.0%	0	0.0%	**258a,b**
	+ve	21	84.0%	7	100%	
splenomegaly	-ve	9	36.0%	3	42.9%	**.740a**
	+ve	16	64.0%	4	57.1%	
Hepatomegaly	-ve	15	60.0%	6	85.7%	**.205a**
	+ve	10	40.0%	1	14.3%	
Left hypochondrial pain	-ve	22	88.0%	7	100%	**.336a,b**
	+ve	3	12.0%	0	0.0%	
B symptoms	-ve	25	100.0%	6	85.7%	**.055a,b**
	+ve	0	0.0%	1	14.3%	
Accidental discovery	-ve	17	68.0%	3	42.9%	**.225a**
	+ve	**8**	**32.0%**	**4**	**57.1%**	

Table 5: Association between LEF Level in studied group and laboratory data.

	LEF.1 Expression						
	Low LEF-1			High LEF-1			P
	Median	Min	Max	Median	Min	Max	
TLC (109/L)	74.0	18.0	234.0	32.0	9.0	124.0	.083b
Lymphocytic count	65.0	10.0	216.0	27.0	6.5	116.0	.102b
Lymphocytes	78	45	92	75	45	96	.324b
HB (gm/dl)	9.8	5.3	13.5	12.0	7.0	13.0	.207b
PLT (109/L)	124	21.0	356.0	111.0	23.0	229.0	.474b
LDH (IU/L)	289	113	534	292	179	442	.721b

Table 6: Association between LEF Level in studied group, laboratory data and Rai staging.

		LEF.1 Expression				
		Low LEF-1		High LEF-1		p
		Count	Column N %	Count	Column N %	
CD19	-ve	2	8.0%	2	28.6%	**.146[a,b]**
	+ve	23	92.0%	5	71.4%	
CD5	-ve	1	4.0%	1	14.3%	**.320[a,b]**
	+ve	24	96.0%	6	85.7%	
CD20	-ve	2	8.0%	2	28.6%	**.146[a,b]**
	+ve	23	92.0%	5	71.4%	
CD23	-ve	3	12.0%	0	0.0%	**.336[a,b]**
	+ve	22	88.0%	7	100.0%	
79b	-ve	13	52.0%	4	57.1%	**.810[a]**
	+ve	12	48.0%	3	42.9%	
FMC7	-ve	22	88.0%	6	85.7%	**.872[a,b]**
	+ve	3	12.0%	1	14.3%	
CD38	-ve	21	84.0%	6	85.7%	**.912[a]**
	+ve	4	16.0%	1	14.3%	
Cyto,17p del	-ve	23	92.0%	7	100.0%	**.440[a,b]**
	+ve	2	8.0%	0	0.0%	
Coombs test	-ve	24	96.0%	7	100.0%	**.591[a,b]**
	+ve	1	4.0%	0	0.0%	
HCV	-ve	20	80.0%	7	100.0%	**.198[a]**
	+ve	5	20.0%	0	0.0%	
Rai stage	0	2	8.0%	0	0.0%	**.707[a,b]**
	1	1	4.0%	1	14.3%	
	2	5	20.0%	1	14.3%	
	3	7	28.0%	3	42.9%	
	4	**10**	**40.0%**	**2**	**28.6%**	

Table 7: Association between LEF Level in studied group, treatment, response to treatment and mortality state

		LEF.1 Expression				
		Low LEF-1		High LEF-1		
		Count	Column N %	Count	Column N %	**P**
Treatment	CHOP/FC	12	9.5%	0	0.0%	**.935[a,b]**
	COP	2	9.5%	1	9.09%	
	COP/FC	10	47.6%	3	27.2%	
	FCR	5	23.8%	7	63.6%	
	FOLLOW	2	9.5%	0	0.0%	
Response	FOLLOW	2	8.0%	0	0.0%	**.356[a,b]**
	Not-Respond	4	16.0%	0	0.0%	
	Respond	19	76.0%	7	100%	
Alive		25	100.0%	5	71.4%	**.006**
Died		**0**	**0.0%**	**2**	**28.6%**	

Table 8: the 2-Year OS rate in relation to LEF-1

OS	**Survival Rate %**		
	2-year OS%	Log Rank	**P**
LEF-1≤9.84	100%	7.7	**0.005**
LEF-1>9.84	71.4%		
Overall	**93.8%**		

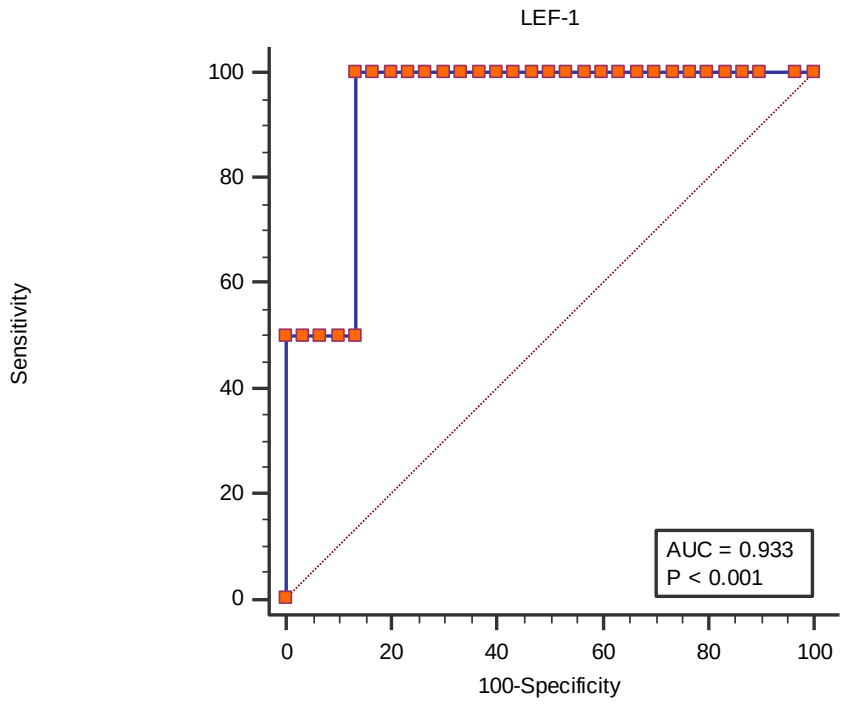

Figure 1: Receiver operating characteristic curve (ROC) and area under the curve (AUC) for LEF-1 at diagnosis for survival analysis

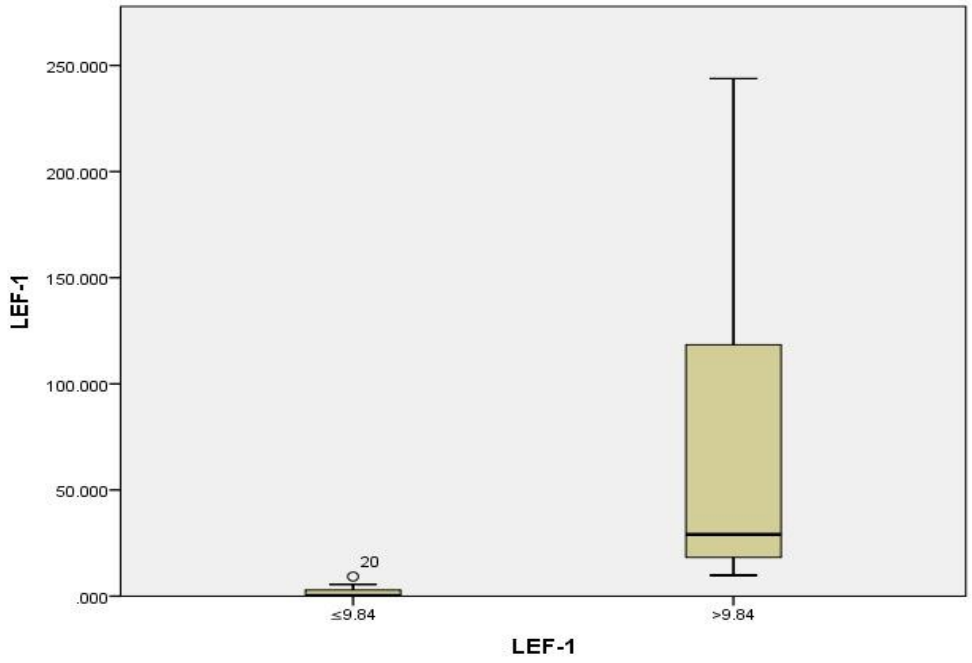

Figure 2: Box-plot diagram representing the range of LEF1 levels in high LEF1 group versus low LEF1 group. Upper and lower lines of each box indicate the 25th and 75th percentiles. The line through each box indicates the median.

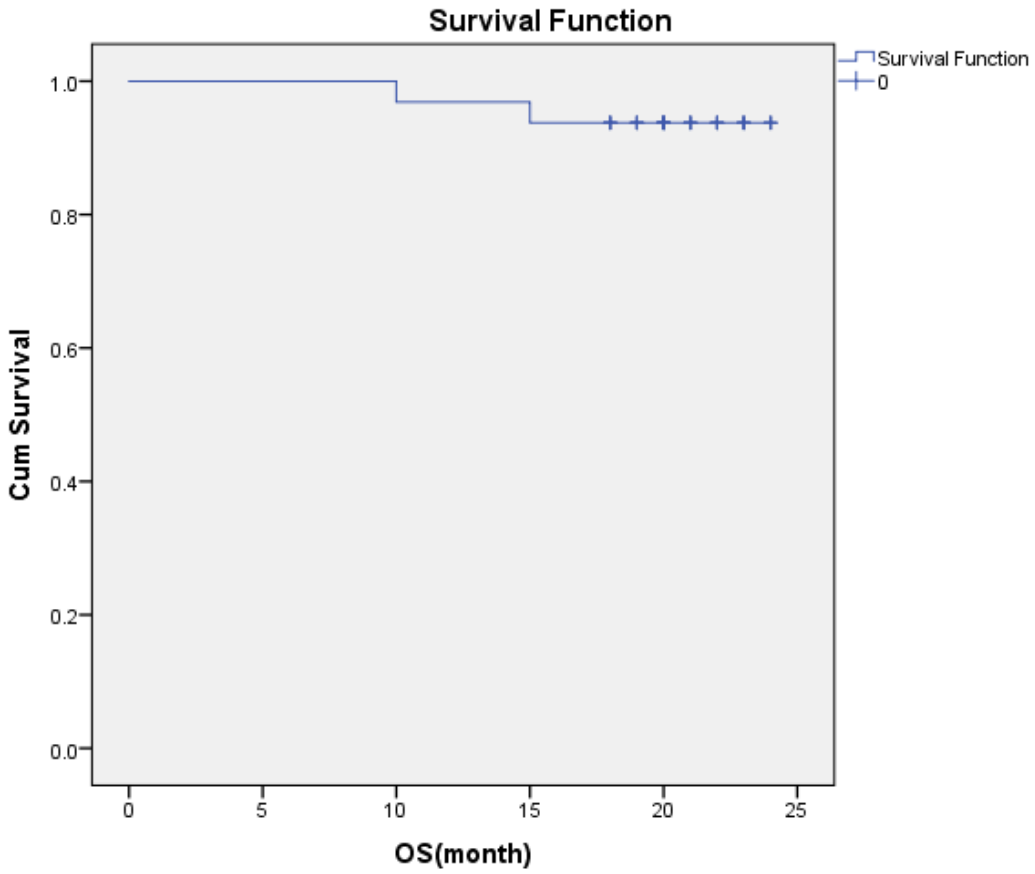

Figure 3: The overall survival in studied group

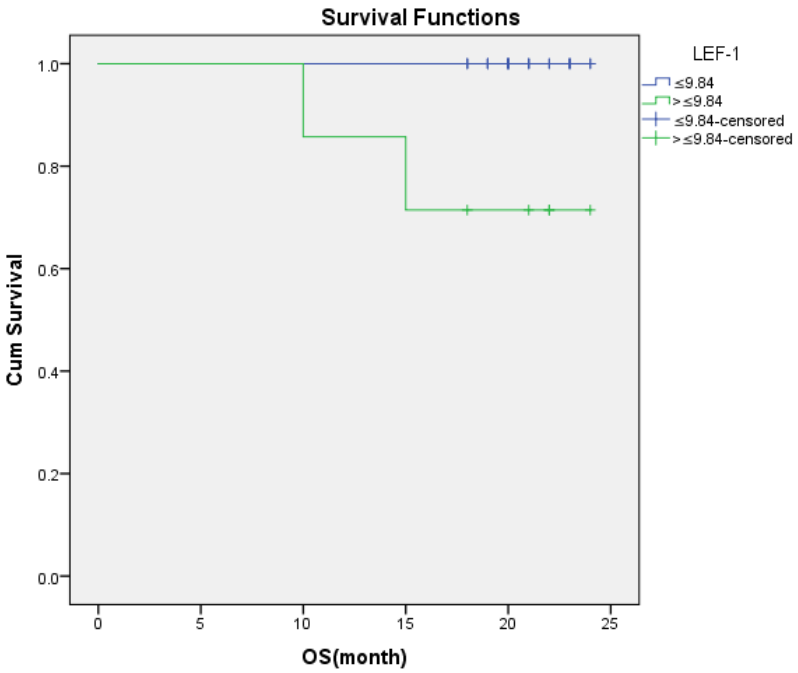

Figure 4: Kaplan– Meier survival curves illustrating the 2-Year OS rate in relation to LEF-1

DISCUSSION

Chronic lymphocytic leukemia (CLL) is the commonest leukemia in western countries. The disease typically occurs in elderly patients and has a highly variable clinical course. Leukemic transformation is initiated by specific genomic alterations that impair apoptosis of clonal B-cells [12]. The diagnosis is established by blood counts, blood smears, and immunophenotyping of circulating B-lymphocytes, which identify a clonal B-cell population carrying the CD5 antigen, as well as typical B-cell markers [13]. A comprehensive, international prognostic score (CLL-IPI) integrates genetic, biological and clinical variables to identify distinct risk groups of CLL patients [14].

Transcription factors are regulatory proteins that either activate or repress the transcription of genes via binding to DNA regulatory sequences and regulating recruitment of transcriptional complexes. Lymphoid enhancer-binding factor 1 (LEF1), a member of the T-cell Factor (TCF)/LEF1 family of high-mobility group transcription factors, is a downstream mediator of the Wnt/β-catenin signaling pathway, but can also modulate gene transcription independently. LEF1 is essential in stem cell maintenance and organ development, especially in its role in epithelial-mesenchymal transition (EMT) by activating the transcription of hallmark EMT effectors including N-Cadherin, Vimentin, and Snail [15]. Aberrant expression of LEF1 is implicated in tumorigenesis and cancer cell proliferation, migration, and invasion. LEF1's activity in particular cancer cell types, such as chronic lymphocytic leukemia (CLL), Burkitt lymphoma (BL), acute lymphoblastic leukemia (ALL), oral squamous cell carcinoma (OSCC), and colorectal cancer (CRC), makes it a valuable biomarker in predicting patient prognosis [15] [16].

This study was carried out on patients newly diagnosed as b-cell chronic lymphocytic leukemia, In El-Sharnouby et al., [17] the study was carried out on newly diagnosed B-CLL patients, in Wu et al., [18] CLL patients were either previously untreated or had received no treatment for at least 6 months before the investigation, while in Erdfelder et al., [19] the study included untreated patients, and patients with a maximum of up to three prior treatment regimens.

According to clinical data of our CLL patients; 53.1% had PS (0) and 46.9% had PS (1). The Rai staging system classifies the patients according to whether a patient has, or does not have, any of the following: Lymphocytosis, Lymphadenopathy, splenomegaly and/or hepatomegaly, anemia or thrombocytopenia. According to the Rai staging of studied group, they were; stage 0 (6.2%), stage 1 (6.2%), stage 2 (18.7%), stage 3 (31.1%) and stage 4 (37.5%). in Wu et al., (2016) [19] stage 0-2were (62%) and stage 3-4 were (38%). in Gutierrez et al., [20] stage 0 (30.9%), stage 1 (26.1%), stage 2 (7.1%), stage 3 (9.8%), stage 4 (4.7%), and (21.4) ND, not determined. Also El-Sharnouby et al., [17], and Erdfelder et al., [19] included all stages. Medical history and clinical examination of patients reveled easy fatigability in 20 patients (62.5%), LN enlargement was positive in 28 patients (87.5%), Splenomegaly was positive in 20

patients (62.5%), Left hypochondrial pain was positive in 3 patients (9.4%) ,Hepatomegaly was positive in 11 patients (34.5%) while B symptoms (fever, night sweats, and weight loss) were positive in 1 patients (3.1%).In El-Sharnouby et al., (2018)[18], lymphadenopathy was observed in 41/45 (91.1%), splenomegaly was observed in 27/45 (60%) and hepatomegaly was observed in 11/45 (24.4%).

Laboratory data showed that TLC (109 / L) (9 - 234) with a Mean±SD (79.1±60.5), absolute lymphocytic count (6.5 – 216 (109 / L)) with a Mean±SD (69.9±56.8), Lymphocytes percentage ranged from 45% to 96% with a Mean±SD (76±13). ALC wasn't so high in some case, yet clonality approved by flow cytometry

In El-Sharnouby et al., [17], TLC (109 / L) (15 – 503) with a Mean±SD (79.8±105.2), absolute lymphocytic count (13.5 – 407 (109 / L)) with a Mean±SD (65.9±84.6). HB (g/dl) ranged from 5.3 to 13.5 with a Mean±SD (9.8±2.3), 23 cases (71% of patients) presented with anemia, 9 cases with mild anemia > 10 g/dl , 7 cases with moderate anemia 8 - 9.9 g/dl and 7 cases with marked anemia < 8 g/dl .We should consider late presentation of many of our cases. About one half of CLL patients are mildly anemic at presentation. Secondary causes of anemia (such as iron, folate or vitamin B12 deficiency) could be presented, Immune hemolytic hypersplenism anemia of chronic diseases and bone marrow failure. One case had Immune hemolytic with positive direct antiglobulin (Coomb's) test. In El-Sharnouby et al., [17], HB (g/dl) ranged from 7.8 to 11.2 with a Mean±SD (9.1±0.88).

PLT count ranged from 21 to 356 (109 / L) with a Mean±SD (139.8±87.8) 6 cases with mild thrombocytopenia > 100, 8 cases with moderate thrombocytopenia 50 - 99 and 5 cases with marked thrombocytopenia < 50. Thrombocytopenia could be due to immune phenomenon, splenic pooling and bone marrow failure. In El-Sharnouby et al., [17], PLT count ranged from 68 to 155 (109 / L) with a Mean±SD (101.3±22.04).

Immunophenotyping is a very important tool in CLL diagnosis; CD19 (87.5%), CD5 (93.8%), CD20 (87.5%), CD23 (90.4%), CD79b (46.9%), FMC7 (12.5%). According to the scoring system, CLL cases are usually >3.

CD38 was positive in (15.6%) of case, while in Gutierrez et al., [20] CD38 was positive in (19%) and in Wu et al., [18] CD38 was positive in (24.3%). CD38 is a strong prognostic marker in CLL as a predictor of survival and aggressive clinical course, Therefore, CD38 expression is a measure of cell division and a reflection of growth in vivo [21]. The 17p deletion was detected in 2 cases (6.3%),while In Gutierrez et al., (2010)[20] detected in 1 case (2.3%) and in Wu et al., (2016)[18] TP53 abnormalities (included 17p deletion or TP53 mutation) detected in 40 cases (26.6%), this higher percentage could be due to inclusion of TP53 mutation.

As regard Induction chemotherapy, 13 patients (40.6%) treated with COP/FC, 3 patients (9.3%) treated with COP, 2 patients (6.2%) treated with FCR and 2 patients (6.2%) treated with CHOP/FC. while 2 patients (6.2%) need no treatment. 26 patients (81.3%) respond to treatment while 4 patients (12.5%) didn't respond. In contrast to our study Wu et al., [18] 80 patients (40%) required no treatment while 117 patients (60%) required treatment. In our study 6.3% of studied group died during the study, they were in high LEF1 group. In Wu et al., [18] 6.5% died during the study, also they were mainly in high LEF1 group.

After a median follow-up period of 20 months (range, 10-24 months), 6.3 % of patients died (2/32 patients). The 2-year overall survival rate was 93.8% with a mean of 23.2± 0.5 months (95% CI; 22.2 – 24.2 months); however, the median OS was not reached. In Wu et al., [18] median OS: LEF1 high, 150 months, LEF1 low, not reached.

There was no significant difference between Low LEF1 group and high LEF1 group as regards gender, age and Rai staging (P >0.05). These results coincide with the results reported by Wu et al., [18]. Erdfelder et al., [19] included patients of all Binet stages; Patients without pretreatment were split in two groups. Group 1 consisted of Binet A stage patients diagnosed less than one year ago. Group 2 included patients in stage Binet C and Binet A/B patients requiring treatment. The patients in the first group showed a mean LEF1 RER (relative expression ratios) of 22.01 whereas those of the second group showed a mean of 85.61. This difference was also highly significant (P<0.001). There was no significant difference between Low LEF1 group and high LEF1 group as regards TLC, absolute lymphocytic count, lymphocytes %, HB level, PLT count, Coombs' Test and LDH (P >0.05), Erdfelder et al., [19] found a significant difference between Low LEF1 group and high LEF1 group as regards lymphocytes % (P<0.001). There was no significant difference between Low LEF1 group and high LEF1 group as regards CD38 and 17p del (P >0.05), Similar to our results, El-Sharnouby et al., [18], Wu et al., [18] and Erdfelder et al., [19] did not observe any significant association between LEF1 expression and CD38 levels, Hence, one possible interpretation of our results is that the prognostic subgroup defined by CD38 positivity is also LEF1 independent. Another possible explanation could be CD38 variability during the

course of CLL, which reduces the LEF1-CD38 correlation.CD38 expression and immunoglobulin variable region mutations are independent prognostic variables in chronic lymphocytic leukemia, but CD38 expression may vary during the course of the disease. Wu et al., [18] didn't find a significant difference between Low LEF1 group and high LEF1 group as regards TP53 abnormalities (included 17p deletion or TP53 mutation) and ZAP70, while they found a significant difference as regards IGHV mutational status. There was no significant difference between low LEF1 group and high LEF1 group as regards treatment and response to treatment (P > 0.05); however, there was a significant difference between Low LEF1 group and high LEF1 group as regards mortality state (P .006). All the patients in low LEF1 group were alive at the end of follow up period, while in high LEF1 group five were alive at the end of follow up period and two died during the study (one in stage 3 and one in stage 4). Wu et al., [18] didn't find a significant difference between Low LEF1 group and high LEF1 group as regards treatment requirement (P > 0.05), however was a significant difference as regards mortality state (P .0101), 6.5% died during the study, also they were more in high LEF1 group (11 patients died in high group while 2 patients died in low group).

The overall survival of patient's low LEF1 level was longer than patients with high LEF1 level. Such difference was statistically significant (P=0.005). Similar to our results Wu et al., [18] stated that overall survival (OS) time were much longer in CLL patients with low LEF1 expression than in those with high LEF1 levels.

CONCLUSION

There was a significant difference between Low LEF1 group and high LEF1 group as regards mortality state (P .006). All the patients in low LEF1 group were alive at the end of follow up period, while in high LEF1 group five were alive at the end of follow up period and two died during the study. The overall survival of patient's low LEF1 level was longer than patients with high LEF1 level. Such difference was statistically significant (P=0.005). For this reason, level of expression of LEF1 in patients with CLL may be effective in predicting the survival.

Conflict of interest: no conflicts of interest. The authors alone are responsible for the content and writing of the paper**.**

Financial disclosure: None declared.

REFERENCES

1. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 2016 ;127(20):2375-90.
2. Ke X, Do DC, Li C, Zhao Y, Kollarik M, Fu Q, et al. Ras homolog family member A/Rho-associated protein kinase 1 signaling modulates lineage commitment of mesenchymal stem cells in asthmatic patients through lymphoid enhancer-binding factor 1. J Allergy Clin Immunol 2019 ;143(4):1560-1574.
3. Bhattacharya M, Sharma AR, Sharma G, Patra BC, Lee SS, Chakraborty C. Interaction between miRNAs and signaling cascades of Wnt pathway in chronic lymphocytic leukemia. J Cell Biochem 2020 ;121(11):4654-4666.
4. Taciak B, Pruszynska I, Kiraga L, Bialasek M, Krol M. Wnt signaling pathway in development and cancer. J Physiol Pharmacol 2018 ;69(2).
5. Grainger S, Traver D, Willert K. Wnt Signaling in Hematological Malignancies. Prog Mol Biol Transl Sci 2018 ;153:321-341.
6. Menter T, Trivedi P, Ahmad R, Flora R, Dirnhofer S, Tzankov A, et al.Diagnostic Utility of Lymphoid Enhancer Binding Factor 1 Immunohistochemistry in Small B-Cell Lymphomas. Am J Clin Pathol 2017 ;147(3):292-300.
7. Joshi, Annada Anil, Alka Vishwas; SHIRSAT, Neelam Vishwanath. Hsa-miR-106b-5p Negatively Regulates LEF1. Journal. Vol, 2018, 6.4: 112-117.
8. Elsourdy M ,Ayad M, Fayad A and Youssef S. Lymphoid enhancer factor 1 gene expression in comparison to other prognostic markers in adult B-acute lymphoblastic leukemia. The Egyptian Journal of Haematology 2019; 44.1: 40.
9. Jia M, Zhao HZ, Shen HP, Cheng YP, Luo ZB, Li SS et al. Overexpression of lymphoid enhancer-binding factor-1 (LEF1) is a novel favorable prognostic factor in childhood acute lymphoblastic leukemia. Int J Lab Hematol 2015 ;37(5):631-40.
10. Feder, Kristin. Dissecting the role of lymphoid enhancer factor 1 (LEF1) in acute myeloid leukemia. 2019. PhD Thesis. Universität Ulm.
11. Fetisov TI, Lesovaya EA, Yakubovskaya MG, Kirsanov KI, Belitsky GA. Alterations in WNT Signaling in Leukemias. Biochemistry (Mosc) 2018 ;83(12):1448-1458.
12. Hallek M. Chronic lymphocytic leukemia: 2020 update on diagnosis, risk stratification and treatment. Am J Hematol 2019 ;94(11):1266-1287.
13. Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Döhner H, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood 2018 ;131(25):2745-2760.
14. International CLL-IPI working group. An international prognostic index for patients with chronic lymphocytic leukaemia (CLL-IPI): a meta-analysis of individual patient data. Lancet Oncol 2016 ;17(6):779-790.
15. Santiago L, Daniels G, Wang D, Deng FM, Lee P. Wnt signaling pathway protein LEF1 in cancer, as a biomarker for prognosis and a target for treatment. Am J Cancer Res 2017;7(6):1389-1406.
16. Zhang Y, Ruan F. LncRNA LEF1-AS1 Promotes Ovarian Cancer Development Through Interacting with miR-1285-3p. Cancer Manag Res 2020 ;12:687-694.

17. El-Sharnouby J A, El-Khamessy G A, Tamer A E and Abd El-Bar E S. The Role of Expression of Lymphoid Enhancer-Binding Factor-1 (LEF-1) in Patients with Chronic Lymphocytic Leukemia. The Medical Journal of Cairo University 2018, 86.September: 2931-2937
18. Wu W, Zhu H, Fu Y, Shen W, Miao K, Hong M et al. High LEF1 expression predicts adverse prognosis in chronic lymphocytic leukemia and may be targeted by ethacrynic acid. Oncotarget 2016 ;7(16):21631-43.
19. Erdfelder F, Hertweck M, Filipovich A, Uhrmacher S, Kreuzer KA. High lymphoid enhancer-binding factor-1 expression is associated with disease progression and poor prognosis in chronic lymphocytic leukemia. Hematol Rep 2010 26;2(1):e3.
20. Gutierrez A Jr, Tschumper RC, Wu X, Shanafelt TD, Eckel-Passow J, Huddleston PM 3rd et al. LEF-1 is a prosurvival factor in chronic lymphocytic leukemia and is expressed in the preleukemic state of monoclonal B-cell lymphocytosis. Blood 2010 ;116(16):2975-83.
21. Malavasi F, Deaglio S, Damle R, Cutrona G, Ferrarini M, Chiorazzi N. CD38 and chronic lymphocytic leukemia: a decade later. Blood 2011;118(13):3470-8.

To Cite:
azab, M., baraka, A., el shorbgy, SH., Abd el-hameed, A., Lymphoid enhancer binding factor-1 (LEF1): as a prognostic factor in patients with Chronic lymphocytic leukemia. *Zagazig University Medical Journal*, 2023; (469-478): -.doi: 10.21608/zumj.2021.89473.2310.