Assessment of the Prognostic Role of Platelets-Lymphocytes and Neutrophil- Monocyte Ratios in Chronic Lymphocytic Leukemia

Mahmoud FH[1], Abd El Rahman MZ[2], Ahmed EHA[3], Zahran AM[3]

[1] Clinical Pathology Department, Faculty of Medicine, New Valley University, Egypt
[2] Clinical Pathology Department, Faculty of Medicine, Assiut University, Egypt
[3] Clinical Pathology Department, South Egypt Cancer Institute, Assiut University, Egypt

Abstract:

Background: The most prevalent form of leukemia in the western world is chronic lymphocytic leukemia (CLL). Today, there is a lot of worry over the evaluation of the platelets-lymphocytes and neutrophil-monocyte ratios in CLL.
Aim of work: To assess platelet –lymphocyte ratio (PLR), neutrophil- monocyte ratio (NMR), neutrophil –lymphocyte ratio (NLR) and lymphocyte –monocyte ratio (LMR) as biomarkers for CLL prognosis and to evaluate the correlation of theses parameters with other established prognostic factors as CD38 and ZAP70 and their correlation with survival outcome of patients with CLL.
Methods: This retrospective study was conducted at medical oncology and clinical pathology departments at south Egypt cancer institute during the period from 2010 to 2020. A total of 142 consecutive CLL patients who admitted to SECI. Of these, only 90 CLL patients had full data, so they were enrolled in the current study. We collected patients' data at diagnosis and after finishing treatment (after three months). The collected data include laboratory data (Complete blood picture, liver function, kidney function, Lactate dehydrogenase and immunophenotyping), clinical data (history and complete clinical examination), imaging data (abdominal ultrasound and Compturized tomography) and outcome data.
Results: Regarding immunophenotyping all patients showed co-expression of CD5, CD19 and CD23. Also, CD200 was expressed in 94.9% of CLL patients, ZAP70 was expressed in 33.3% of CLL patients, CD38 was expressed in 60.7%, 35.4% of CLL patients had Kappa light chain restriction while 60.4% had Lambda light chain restriction. The studied CLL cases have significantly lower PLR, NMR, and NLR levels and higher LMR level than that of matched controls. After three months of treatment, PLR, NMR, and NLR biomarkers levels were significantly increased and LMR was decreased.
Conclusion: At the time of diagnosis, patients with CLL have abnormal haematological biomarkers (PLR, NMR, NLR, and LMR), which are normalized by treatment. In CLL patients, increased PLR, NMR, and NLR play a positive predictive impact.

Keywords: Chronic lymphocytic leukemia, Platelet lymphocyte ratio, Neutrophil monocyte ratio.

Received: 18 September 2023
Accepted: 6 December 2023

Authors Information:
Fatma Hussein Mahmoud
Clinical Pathology Department, Faculty of Medicine, New Valley University, Egypt
email: Fh449615@gmail.com

Mohamed Zakaria Abd El Rahman
Clinical Pathology Department, Faculty of Medicine, Assiut University, Egypt
email: M-Z-abokrisha@gmail.com

Eman Hassan Ahmed
Clinical Pathology Department, South Egypt Cancer Institute, Assiut University, Egypt
email: Ehasan888@gmail.com

Asmaa Mohamed Zahran
Clinical Pathology Department, South Egypt Cancer Institute, Assiut University, Egypt

Corresponding Author:
Fatma Hussein Mahmoud
Clinical Pathology Department, Faculty of Medicine, New Valley University, Egypt
email: Fh449615@gmail.com

Introduction:

The most prevalent form of leukemia in the western world is chronic lymphocytic leukemia (CLL). The National Cancer Registry indicated that more than 80% of lymphoid leukemias in Egypt are CLL, making it the most prevalent subtype of leukemia. The majority of adult patients with leukemia are diagnosed with it[1].Clonal CD19-positive B cells called CLL lymphocytes are characterized by an overabundance of CD5-positive monoclonal B cells in peripheral blood. Aspiration of the bone marrow reveals a lymphocytic replacement of the normal marrow components, of

which lymphocytes make up 25–95%. A trephine biopsy indicates lymphocyte infiltration that is nodular, diffuse, or interstitial [2].

Guidelines from the European Society of Medical Oncology and the International Workshop on Chronic Lymphocytic Leukemia both demand that lymphocytosis remain for more than three months. Clinical staging systems are the most crucial prognostic indicators in CLL [3]. These systems are based on clinical examination, such as lymphadenopathy and organomegaly, peripheral blood results (platelet and hemoglobin values), tumour load markers (thymidine kinase and B2-microglobulin), expression of specific proteins in CLL cells (CD38, CD49d, and ZAP-70), genetic abnormalities measured by fluorescence in situ hybridization (FISH), such as del(13q), tri12, del(11q), and del(17p)[4].

Lastly, prognosis in patients with CLL should consider treatment response as well as disease progression and overall survival. The biological basis for the platelet-lymphocyte ratio (PLR) calculation comes from the common occurrence of an increase in the lymphocyte count and a decrease in the platelet count in later stages of CLL. Therefore, we hypothesized that the ratio using both the platelet and lymphocyte counts may have a prognostic role in patients with CLL. Neutrophil-monocyte ratio (NMR), Neutrophil-to-lymphocyte (NLR) and lymphocyte-to-monocyte ratio (LMR) could be used as biomarkers for CLL prognosis and therefore it will be used to prove its relationship with disease severity and its prognostic values [3].

Aim of work:

To assess PLR, NMR, NLR and LMR as biomarkers for CLL prognosis and to evaluate the correlation of theses parameters with other established prognostic factors as CD38 and ZAP70 and their correlation with survival outcome of patients with CLL.

Methods:

This retrospective study was conducted at South Egypt Cancer Institute (SECI) over a period of ten years during the period between the 1st of January 2010 up to end of January 2020. With reviewing medical records of patients admitted to SECI in this period, one hundred and forty-two (142) patients were diagnosed as CLL, and ninety (90) patients were included in this study who were available with full clinical and laboratory data at base line and follow up. The study included also forty (40) age and sex matched controls (not malignant, not diabetic, or hypertensive). The approval of the ethical committee of Faculty of Medicine, Assiut University was obtained before we started (IRP: 17100981). We evaluated patients' data at diagnosis and after finishing treatment (after three months). The collected data for cases include complete blood count (CBC), liver function, kidney function, lactate dehydrogenase (LDH) and immunophenotyping and for control CBC and LDH were done. Cases who started their treatment outside SECI or who did not have complete clinical and laboratory data at presentation and follow up were excluded. Data at presentation included history and complete clinical examination were collected. Data of imaging including abdominal ultrasound and computed tomography (CT) scans were performed to assess organomegaly (splenomegaly and hepatomegaly), also to detect number and size of enlarged lymph nodes. To help assess severity of CLL, Rai staging was used to subdivide Patients to five different stages: (stage 0, stage I, stage II, stage III, and stage IV). The patients were then subdivided into two groups (early and advanced): early group include stage 0, I, II and advanced group include stage III, IV. CBC was done on automated cell counters were used; Ruby Cell Dyn 1700 (Serial number: 513554) and ABX pentra DF Nexus (serial number: 605PNF0694). Hemoglobin, platelet count, mean platelet volume (MPV), total leukocytic count, relative and absolute count of (neutrophil, lymphocytes, and monocytes) were recorded. Other investigations were recorded as liver function, kidney function and LDH which were done by Cobas integra 400 plus (swiss, serial number: 500558) and Dimension X Pand Plus (serial number: 2004082965). Regarding immunophenotyping, the data were reported and found to be processed and analyzed using the Becton Dickinson fluorescence activated cell sorter FACSCaliber (serial number: E5140) and FACScanto II (serial number: V33896201978) according to standard procedures. Lymphoma panelincluded CD3, CD4, CD8, CD5, CD10, CD19, CD23, CD20, CD200, FMC7, CD79b, Kappa, Lambda, IGM, CD38 and ZAP70.

Statistics/data analysis:

All statistical calculations were done using SPSS (statistical package for the social science; SPSS Inc., Chicago, IL, USA) version 22. Data were statistically described in terms of mean ± standard deviation (±SD), or median and range, frequencies (number of cases) and relative frequencies (percentages) when appropriate. Quantitative data was analyzed by using student t test for normally distributed data and Mann Whitney U test for non-normally distributed data and Wilcoxon sign rank test was used for comparing paired data. For comparing categorical data, Chi square ($\chi 2$) test was performed. Exact test was used instead when the expected frequency is less than 5. A correlation between various variables was done using the Spearman rho test. Hazard ratio (HR) with 95% Confidence Interval (CI) and COX regression analysis was calculated to determine significant factors associated with mortality. The P-value set significant at 0.05 level.

Results:

Regarding the demographic data in our study, the mean age of the studied participants was 60.73 ± 9.51 years and ranged from 42 up to 80 years. Out of 90 studied cases; 55 cases (61.1%) were males, and 35 cases (38.9%) were females. Based on RAI staging, there were 3 patients in stage 0, 11 in stage I, 5 in stage II, 30 in stage III and 41 in stage IV. According to

classification of patients into early and late groups, 78.9% of patients suffered from advanced tumor stage which include RAI stage III and stage IV [5](Table 1). A significant difference was observed between both patients and controls regarding all CBC parameters except for MPV which was comparable between CLL patients and control with no significant difference between them. Also we observed that the studied CLL cases have significantly lower PLR, NMR, and NLR levels and significantly higher LMR level compare to the control group (Table 2). Regarding immunophenotyping all patients showed coexpression of CD5, CD19 and CD23. Also, CD200 was expressed in 94.9% of CLL patients, ZAP70 was expressed in 33.3% of CLL patients, CD38 was expressed in 60.7%, 35.4% of CLL patients had Kappa light chain restriction while 60.4% had Lambda light chain restriction (Table 3). The studied CLL cases have significantly lower PLR, NMR, and NLR levels and higher LMR level than that of matched controls. After treatment, PLR, NMR, and NLR biomarkers levels were significantly increased and LMR was decreased. Also, PLR, NLR in addition to NMR were significantly higher in CLL 51 patients who achieve remission after three months of treatment compared to 39 patients who didn't achieve remission (Table 6). No significant correlation was observed between any of the studied hematological biomarkers and ZAP70 or CD38 (Table 5). Also, these hematological biomarkers have no role in predicting survival in CLL patients (Table 7). The best cut off, sensitivity and specificity of the studied hematological biomarkers as prognostic markers for detection of patient's response in chronic lymphocytic leukemia are demonstrated in (Table 8) and (Figure 1).

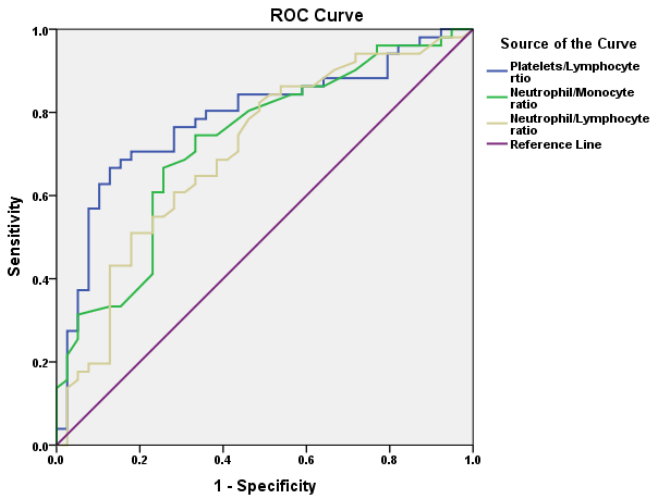

Figure (1): ROC curves for detection of CLL patient's response. PLR (blue), NMR (green), NLR (brown) and Reference line (purple). For PLR; area under the curve = 0.787 (0.69 to 0.88), ***P*** value < 0.001, for NMR; area under the curve = 0.728 (0.62 to 0.83), ***P*** value < 0.001, and for NLR; area under the curve = 0.706 (0.59 to 0.82), ***P*** value = 0.001.

Table (1): Demographic and clinical characteristic of patients with CLL and the controls

Variable name	CLL cases (n=90)		Controls (n=40)		*P* value
Age (years)					0.061
• Mean ± SD	60.73 ± 9.51		57.50 ± 7.77		
• Range	42 – 80		41 - 75		
Sex					0.330
• Male	55	(61.1%)	28	(70.0%)	
• Female	35	(38.9%)	12	(30.0%)	
Clinical presentation					
• LN enlargement	70	(77.8%)			
• Hepatomegaly	44	(48.9%)			
• Splenomegaly	46	(51.1%)			
• Hepatosplenomegaly	35	(38.9%)			
Rai staging					
• Stage 0	3	(3.3%)			
• Stage I	11	(12.2%)			
• Stage II	5	(5.6%)			
• Stage III	30	(33.3%)			
• Stage IV	41	(45.6%)			

CLL: chronic lymphocytic leukemia. Data are presented as mean ± SD and range, or number and percentage. Student t test was used for comparing continuous data, and Chi square ($\chi 2$) test for comparing categorical data**.** ***p*** value is significant if ≤0.05.

Table (2): Comparison of laboratory data between patients with CLL and the controls

Laboratory data	CLL patients (n=90) Median (range)	Controls (n=40) Median (range)	*P* value
• LDH (U/L)	547.5 (130.0 - 1336.0)	262.0 (159.0 – 350.0)	**<0.001**
• WBCs (10^3/ul)	55.6 (10.6 - 490.0)	5.9 (4.2 – 11.0)	**<0.001**
• Relative neutrophils (%)	10.0 (2.0 - 41.0)	59.0 (45.0 – 64.0)	**<0.001**
• Absolute neutrophils (10^3/ul)	5.1 (1.1 - 46.6)	3.5 (1.9 – 6.5)	**<0.001**
• Relative lymphocyte (%)	84.5 (46.0 - 97.0)	33.0 (28.0 – 46.0)	**<0.001**
• Absolute lymphocyte (10^3/ul)	38.4 (7.2 - 441.0)	1.9 (1.4 – 3.9)	**<0.001**
• Relative monocyte (%)	4 (1 – 20)	8 (4 – 10)	**<0.001**
• Absolute monocyte (10^3/ul)	1.8 (0.21 - 29.4)	0.4 (0.3 – 0.8)	**<0.001**
• Haemoglobin (gm/dl)	11.1 (5.0 - 15.6)	14.2 (12.1 – 16.0)	**<0.001**
• MPV (fL)	8.6 (5.5 - 12.9)	9.2 (5.2 – 12.0)	0.151
• Platelets (10^3/ul)	150 (15 – 403)	251 (166 – 410)	**<0.001**
• PLR	4.26 (0.21 – 34.84)	142.4 (47.0 – 190.5)	**<0.001**
• NMR	2.5 (0.17 – 19.0)	7.6 (4.6 – 16.0)	**<0.001**
• NLR	0.12 (0.02 – 0.80)	1.79 (0.98 – 2.21)	**<0.001**
• LMR	18.2 (1.3 – 97.0)	4.4 (2.8 – 9.0)	**<0.001**

LDH: Lactate dehydrogenase; WBCs: white blood cells; MPV: mean platelets volume; PLR: Platelets/Lymphocyte ratio; NMR: Neutrophils/Monocyte ratio; NLR: Neutrophil/Lymphocyte ratio; LMR: Lymphocyte/Monocyte Ratios. Quantitative data are presented as median (range). ***p*** value is significant ≤0.05. Mann Whitney U test was used for comparing continuous data.

Table (3): Flowcytometric data of the patients with CLL

Flowcytometric	Negative, n (%)		Positive, n (%)	
• **CD5**	0	(0.0%)	90	(100.0%)
• **CD10**	90	(100.0%)	0	(0.0%)
• **CD19**	0	(0.0%)	90	(100.0%)
• **CD4**	54	(100.0%)	0	(0.0%)
• **CD8**	54	(100.0%)	0	(0.0%)
• **CD3**	54	(100%)	0	(0%)
• **CD23**	0	(0.0%)	90	(100.0%)
• **FMC7**	90	(100.0%)	0	(0.0%)
• **IgM**	42	(67.7%)	20	(32.2%)
• **CD20**	5	(8.7%)	52(dim)	(91.2%)
• **CD200**	0	(0.0%)	90	(100.0%)
• **ZAP70**	34	(66.6%)	17	(33.3%)
• **CD38**	20	(39%)	31	(60.7%)
• **CD79b**	51	(89.4%)	6(dim)	(10.5%)
• **Kappa**	31	(64.5%)	17	(35.4%)
• **Lambda**	19	(39.5%)	29	(60.4%)
• **Co-expression of CD5 and CD 19**	0	(0.0%)	90	(100.0%)
• **Co-expression of CD19 and CD 23**	0	(0.0%)	90	(100.0%)

Data are presented as number and percentage.

Table (4): Comparison of laboratory data of the patients with CLL at baseline and follow up

Laboratory data	Baseline data	Follow up (after 3 months)	*P* value
	Median (range)	Median (range)	
• LDH (U/L)	547.5 (130.0 - 1336.0)	363.0 (110.0 – 1892.0)	0.450
• WBCs (10^3/ul)	55.6 (10.6 - 490.0)	8.8 (2.9 - 337.0)	**<0.001**
• Relative neutrophils (%)	10.0 (2.0 - 41.0)	37.0 (2.0 - 76.0)	**<0.001**
• Absolute neutrophils (10^3/ul)	5.1 (1.1 - 46.6)	3.3 (1.1 - 20.2)	**<0.001**
• Relative lymphocyte (%)	84.5 (46.0 - 97.0)	53.0 (17.0 - 95.0)	**<0.001**
• Absolute lymphocyte (10^3/ul)	38.4 (7.2 - 441.0)	4.4 (0.8 - 299.9)	**<0.001**
• Relative monocyte (%)	4 (1 – 20)	6 (1 – 17)	**0.002**
• Absolute monocyte (10^3/ul)	1.8 (0.21 - 29.4)	0.6 (0.2 - 16.9)	**<0.001**
• Hemoglobin (gm/dl)	11.1 (5.0 - 15.6)	10.8 (7.0 - 15.5)	0.306
• MPV (fL)	8.6 (5.5 - 12.9)	8.6 (6.3 - 10.5)	0.647
• Platelets (10^3/ul)	150 (15 – 403)	175 (8 – 437)	**0.024**
• PLR	4.26 (0.21 – 34.84)	42.56 (0.15 – 263.41)	**<0.001**
• NMR	2.5 (0.17 – 19.0)	4.60 (0.40 – 26.50)	**<0.001**
• NLR	0.12 (0.02 – 0.80)	0.66 (0.02 – 4.47)	**<0.001**
• LMR	18.2 (1.30 – 97.0)	9.00 (1.33 – 95.0)	**<0.001**

LDH: Lactate dehydrogenase; WBCs: white blood cells; MPV: mean platelets volume; PLR: Platelets/Lymphocyte ratio; NMR: Neutrophils/Monocyte ratio; NLR: Neutrophil/Lymphocyte ratio; LMR: Lymphocyte/Monocyte Ratios. Quantitative data are presented as median (range). ***p*** value is significant ≤0.05. The Wilcoxon sign rank test was used for comparing paired continuous data.

Table (5): Correlations between the studied hematological biomarkers and the other prognostic factors among studied patients with CLL

		PLR	NMR	NLR	LMR
ZAP70	**R**	-0.220	-0.022	-0.047	-0.091
	***p* value**	0.120	0.881	0.742	0.525
CD38	**R**	-0.063	0.035	0.030	-0.059
	***p* value**	0.662	0.807	0.835	0.682

PLR: Platelets/Lymphocyte ratio; NMR: Neutrophils/Monocyte ratio; NLR: Neutrophil/Lymphocyte ratio; LMR: Lymphocyte/Monocyte Ratios. Significance defined by ***p***< 0.05, r=Spearman correlation coefficient.

Table (6): Relation between the studied hematological biomarkers and the response status of the studied patients with chronic lymphocytic leukemia

	Patients who achieve remission (n=51)	Patients who not achieve remission (n=39)	*P* value
PLR			**<0.001**
• Mean ± SD	8.83 ± 7.19	3.17 ± 3.86	
• Median (range)	7.9 (0.49 – 34.84)	1.8 (0.21 – 21.46)	
NMR			**<0.001**
• Mean ± SD	4.38 ± 3.56	2.20 ± 1.91	
• Median (range)	3.0 (0.4 – 19.0)	1.7 (0.17 – 9.0)	
NLR			**0.001**
• Mean ± SD	0.22 ± 0.18	0.13 ± 0.15	
• Median (range)	0.17 (0.02 – 0.75)	0.07 (0.02 – 0.80)	
LMR			0.748
• Mean ± SD	27.01 ± 22.66	27.08 ± 24.58	
• Median (range)	20.0 (1.3 – 97.0)	18.0 (2.7 – 97.0)	

PLR: Platelets/Lymphocyte ratio; NMR: Neutrophils/Monocyte ratio; NLR: Neutrophil/Lymphocyte ratio; LMR: Lymphocyte/Monocyte Ratios. Qualitative data are presented as mean ± SD and median (range). Significance defined by ***p*** < 0.05. Mann Whitney U test was used for comparing continuous data.

Table (7): Results of COX regression analysis for predicting likelihood of outcome according to clinic-pathological characteristics of CLL patients

Variable name	B	S.E.	*P* value	HR	95% C.I. for HR
Age groups					
• < 60 years				ref	
• ≥ 60 years	0.196	0.267	0.462	1.217	0.722 – 2.051
Sex					
• Male				ref	
• Female	0.293	0.256	0.253	1.340	0.811 – 2.213
Stage					
• Early				ref	
• Advanced	0.682	0.363	0.060	1.978	0.971 – 4.028
PLR (per unit increase)	-0.007	0.017	0.669	0.993	0.960 – 1.027
NMR (per unit increase)	0.024	0.035	0.500	1.024	0.956 – 1.097
NLR (per unit increase)	-0.242	0.658	0.713	0.785	0.216 – 2.850
LMR (per unit increase)	-0.002	0.005	0.694	0.998	0.989 – 1.008

PLR: Platelets/Lymphocyte ratio; NMR: Neutrophils/Monocyte ratio; NLR: Neutrophil/Lymphocyte ratio; LMR: Lymphocyte/Monocyte ratio. B: regression coefficient; SE: standard error; HR: hazard ratio; CI: confidence interval. p value is significant ≤0.05.

Table (8): ROC curve analysis of the studied parameters

	Cut off	95%CI	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC	*P* value
PLR	≥ 3.1	0.69–0.88	76.5%	66.7%	75.0%	68.4%	72.2%	0.787	**<0.001**
NMR	≥ 2.2	0.62–0.83	70.9%	66.7%	73.5%	63.4%	68.9%	0.728	**<0.001**
NLR	≥ 0.11	0.59–0.82	66.7%	61.5%	69.4%	58.5%	64.4%	0.706	**0.001**

PLR: Platelets/Lymphocyte ratio; NLR: Neutrophil/Lymphocyte ratio; AUC: Area under the curve; CI: confidence interval; PPV: positive predictive value; NPV: negative predictive value. *Significance defined by p< 0.05.

Discussion:

In this study we aimed to assess PLR and NMR as biomarkers for CLL prognosis, and to determine the correlation of theses parameters with other established prognostic factors as CD38 and ZAP70, in addition to determine the effect of these parameters on survival outcome of CLL patients. From January 2010 through January 2020, a total of 142 consecutive CLL patients were admitted to South Egypt Cancer Institute. Of these, only 90 of them have full data; so, included in this study and 40 age and sex-matched controls were also enrolled in the current study. Regarding the demographic data in our study, the mean age of the studied participants was 60.73 ± 9.51 years and ranged from 42 up to 80 years. Out of 90 studied cases; 55 cases (61.1%) were males, and 35 cases (38.9%) were females. Melton & Pearlman reported a similar finding, stating that men outnumbered women 2:1 in the median age of CLL illness onset, which was 67 years old [6]. Also, in Asian countries, Ko et al. (2021) reported that the mean age of the studied cases at diagnosis varied from 66.3 years to 68.6 years and ranged from 66 to 70 years [7]. Based on RAI staging, there were 3 patients in stage 0, 11 in stage I, 5 in stage II, 30 in stage III and 41 in stage IV. According to classification of patients into early and late groups, 78.9% of patients suffered from advanced tumor stage which include RAI stage III and stage IV. This is in line with the current study, Yokus et al. (2020) which observed that according to the modified Rai Staging; 25.4% of the studied CLL cases were considered as low-risk, 48.6% as intermediate- and 26% as high-risk groups [8].

At diagnosis, we observed that CLL cases have significantly higher LDH compared to matched controls. LDH is one of the most common serum markers, this enzyme is increased in CLL as well as other lymphomas, and where a higher level corresponds to several poor-prognostic features, also CLL patients had significantly lower PLR level than that of the matched controls, this is could be explained by absolute lymphocytosis and low platelet count than that of controls. The first and foremost laboratory abnormality found in CLL is lymphocytosis in peripheral blood [8, 9]. The substantial rise in lymphocyte count in our CLL

patients as opposed to neutrophil count may account for the reduced NLR seen in the examined CLL individuals. An inflammatory biomarker called LMR shows when the host immune system and the tumour microenvironment are in equilibrium. In the current investigation, we found that compared to matched controls, CLL cases had considerably higher LMR levels. The significant lymphocytosis seen in CLL patients explains these findings of low LNR and high LMR. The diagnostic threshold for CLL is >=5000/mcL B lymphocytes on peripheral smear, and the majority of patients have an absolute lymphocyte count of >10,000/mcL when they first appear [9]. To the best of our knowledge, no previous study discussed the role of PLR, NMR, NLR and LMR in prediction of CLL diagnosis.

Following a three-month follow-up, the PLR level was noticeably higher than it had been at diagnosis, and it was higher in those who had experienced remission than in people who had not. Additionally, it was more prevalent in patients with early tumour stage than advanced tumour stage. These findings, which are in contrast to those described for non-Hodgkin's lymphoma and solid tumours, may point to a positive prognostic function for PLR in CLL patients. PLR was significantly linked to a poor prognosis in non-Hodgkin's lymphoma patients receiving R-CHOP [10]. Also, Seo et al. (2017) found that when patients with advanced stage marginal zone lymphoma received rituximab, vincristine, cyclophosphamide, and prednisone treatment, PLR demonstrated independent importance [11].

After the follow-up period, the level of NMR and NLR dramatically rose. Additionally, individuals who achieve remission have much greater NMR and NLR levels than patients who do not. Additionally, NMR was equivalent in patients with early and advanced tumour stages, with no discernible difference between them, but NLR is much greater in patients with early tumour stages. Given that the circulating neutrophils from CLL patients were found to have decreased bactericidal activity, likely as a result of myeloperoxidase deficiency and impaired migratory skills, this may suggest a positive predictive role for high NMR&NLR [12]. No significant correlation was observed between any of the studied hematological biomarkers and ZAP70 or CD38. Because higher levels of CD38 and ZAP70 expression on CLL cells are linked to a poor clinical outcome and shorter overall survival [13].

Conclusion and Recommendations:

At the time of diagnosis, patients with CLL have abnormal hematological biomarkers (PLR, NMR, NLR, and LMR), which are normalized by treatment. In CLL patients, increased PLR, NMR, and NLR play a positive predictive impact. Higher PLR and NLR were linked to early tumour stage of CLL. No role is played by the PLR, NMR, NLR, and LMR in determining the prognosis of CLL patients.

List of abbreviations:

CLL: Chronic lymphocytic leukemia.
NMR: Neutrophil-monocyte ratio.
PLR: Platelet-lymphocyte ratio.
FISH: Fluorescence in situ hybridization.
NLR: Neutrophil-to-lymphocyte.
LMR: Lymphocyte-to-monocyte ratio.
SECI: South Egypt Cancer Institute.
CBC: Complete blood count.
LDH: Lactate dehydrogenase.
CT: Computed tomography.
MPV: Mean platelet volume.
SPSS: Statistical package for the social science.
SD: Standard deviation.
HR: Hazard ratio.
CI: Confidence Interval.

Competing interests:

The authors declare that they have no competing interests.

Authors' contributions:

H.B.H.: Conceptualization, Supervision, Investigation, Writing-review & editing. E.M.N.: Supervision, Investigation, Writing -review & editing. M.B.M.: Methodology, Investigation, Data curation, Writing-original draft. M.G.E.: Conceptualization, Methodology, Validation, Investigation, Data curation, Writing- original draft, Supervision. All authors have read and approved the manuscript.

Ethics approval and consent to participate:

The approval of the ethical committee of the Institutional Review Board of Faculty of Medicine, Assiut University was obtained before we started (IRP: 17100981). Our study conformed to all requirements as governed by the declaration of Helsinki.

References:

1) Ibrahim AS, Khaled HM, Mikhail NN, et al. Cancer incidence in Egypt: results of the national population-based cancer registry program. J Cancer Epidemiol. 2014;2014:437971.
2) Bertilaccio MT, Scielzo C, Muzio M, et al. An overview of chronic lymphocytic leukaemia biology. Best Pract Res Clin Haematol. 2010 Mar;23(1):21-32.
3) Eichhorst B, Robak T, Montserrat E, et al. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. Ann Oncol. 2021 Jan;32(1):23-33.
4) Zenz T, Fröhling S, Mertens D, et al. Moving from prognostic to predictive factors in chronic lymphocytic leukaemia (CLL). Best Pract Res Clin Haematol. 2010 Mar;23(1):71-84.
5) Hallek M, Al-Sawaf O. Chronic lymphocytic leukemia: 2022 update on diagnostic and therapeutic procedures. Am J Hematol. 2021 Dec 1;96(12):1679-1705.
6) Melton MF, Pearlman AN. Chronic lymphocytic leukemia of the oropharyngeal cavity and

paranasal sinuses: a case series and literature review. Int Forum Allergy Rhinol. 2015 Nov;5(11):1055-8.

7) Ko BS, Chen LJ, Huang HH, et al. Epidemiology, treatment patterns and survival of chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL) in Taiwan, 2006-2015. Int J Clin Pract. 2021 Aug;75(8):e14258.
8) Yokus O, Saglam EN, Goze H, et al. Prognostic role of lymphocyte/monocyte ratio in chronic lymphocytic leukemia. J Hematol. 2020 Dec;9(4):116-122.
9) Mukkamalla SK, Taneja A, Malipeddi D, et al. Chronic Lymphocytic Leukemia. 2023 Mar 7. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023; 89-93.
10) Kang HJ, Kim WS, Kim SJ, et al. Phase II trial of rituximab plus CVP combination chemotherapy for advanced stage marginal zone lymphoma as a first-line therapy: Consortium for Improving Survival of Lymphoma (CISL) study. Ann Hematol. 2012 Apr;91(4):543-51.
11) Seo J, Kim WS, Kim JS, et al. Platelet to lymphocyte ratio (PLR) retains independent prognostic significance in advanced stage marginal zone lymphoma patients treated with rituximab, cyclophosphamide, vincristine, and prednisone combination chemotherapy (R-CVP): Consortium for Improving Survival of Lymphoma trial. Blood Res. 2017 Sep;52(3):200-206.
12) Itälä M, Vainio O, Remes K. Functional abnormalities in granulocytes predict susceptibility to bacterial infections in chronic lymphocytic leukaemia. Eur J Haematol. 1996 Jul;57(1):46-53.
13) Paulus A, Malavasi F, Chanan-Khan A. CD38 as a multifaceted immunotherapeutic target in CLL. Leuk Lymphoma. 2022 Oct;63(10):2265-2275.