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Low platelet to lymphocyte ratio and high platelet distribution width have an inferior outcome in chronic lymphocytic leukaemia patients

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Introduction. Chronic lymphocytic leukaemia (CLL) is an incurable disease of the elderly, characterised by gradual accumulation of small mature B lymphocytes which escape apoptosis through inflammatory signals from the microenvironment. Elevated inflammatory markers are associated with very poor prognosis in different types of cancer. Therefore, we examined retrospectively the impact of platelet lymphocyte ratio (PLR) and platelet distribution width (PDW) on 180 CLL patients' outcome.

Materials and methods. This retrospective study included 180 patients with CLL who were diagnosed and selected among cases referred to the Oncology Center Mansoura University between January 1st, 2008 and June 30th, 2016. All the relevant information was collected from the electronic medical records of the selected patients.

Results. Our results revealed that low PLR (<2.5) was more frequently observed in patients with stage C ($p < 0.001$), with 17p deletion ($p = 0.017$), and CD38 expression ($p = 0.08$), but not with seropositive HCV patients ($p = 0.2$). High PDW (≥18.5 fl) was more frequently associated with intention to treat population ($p = 0.038$), and CD38 expression ($p = 0.068$), but not with 17p deletion ($p = 0.25$) and seropositive HCV patients ($p = 0.4$). Multivariate analysis for overall survival showed that stage A and low PDW were independent factors for overall survival ($p = 0.014$ and 0.04 respectively), while high PLR ($p = 0.05$), and seronegative HCV patients ($p = 0.1$) lost their significance.

Conclusion. Our data showed that low PLR and high PDW were associated with poor prognostic markers. Stage C-CLL and high PDW were independent predictors of survival.

Key words: chronic lymphocytic leukaemia, platelet distribution width, platelet-to-lymphocyte ratio

Introduction

Chronic lymphocytic leukaemia (CLL) is an incurable disease that is characterized by gradual accumulation of small mature B lymphocytes [1]. These lymphocytes are dormant replicational cells that accumulate in the marrow and peripheral blood, due to extrinsic survival signals from the microenvironment [2].

These leukaemic lymphocytes can resist apoptosis by inflammatory signals compared to normal B lymphocytes. Actually, CLL patients present with manifestations that typically occur in chronic inflammatory disorders which make the role of inflammation clear [3]. Thrombocytopenia in CLL patients caused by either bone marrow infiltration, immune thrombocytopenia, hypersplenism, or myelosuppression secondary to cytotoxic

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therapy or infection [4]. PLR is a novel inflammatory marker that can be applied in many diseases for predicting inflammation, and PDW represents the platelet anisocytosis and is calculated from the distribution of individual platelet volumes [5].

Further, platelet-to-lymphocyte ratio (PLR) finds its role in CLL that the lymphocyte and platelet counts are correlated to the pathogenesis of CLL directly and affect management of patients. Also, PDW does not assess heterogeneity of platelet volume only, but also platelet activity [6]. Many studies have shown that these two inflammatory biomarkers (PLR and PDW) are considered prognostic factors for some non-haematological tumours [5].

To our knowledge, PDW has not been studied in CLL. So, in our study, we aimed at investigating the role of PLR and PDW in our CLL patients.

Materials and methods

Subjects

This retrospective study included 180 patients with CLL who were diagnosed and selected among cases referred to the Oncology Center Mansoura University (OCMU) between January 1th, 2008 and June 30th, 2016. All the relevant information was obtained through the electronic medical records of the selected patients. All laboratory procedures were performed in the clinical pathology labs of OCMU. The Binet staging system was used to classify the CLL patients:

- Binet stage A: <3 areas of lymphoid tissue are enlarged, with no anaemia or thrombocytopenia.
- Binet stage B: ≥3 areas of lymphoid tissue are enlarged, with no anaemia or thrombocytopenia.
- Binet stage C: anaemia (<10 g/dL) and/or thrombocytopenia (<100 × 10^9/L) are present. Any number of lymphoid tissue areas may be enlarged.

They were treated according to our institute guidelines based on performance statue by purine based regimen or alkylators. As far as we know, patients with immune-related cytopenia or infection were excluded from our study.

Patient evaluation

Detailed history taking and clinical examination. Laboratory investigations:

1. Routine work:

- Complete blood count (haemogram): using the electronic counter (CELL-DYN 3700, Abbott, Canada), PDW and PLR were obtained, before any treatment, including PDW (fl), the lymphocyte count (k/uL) and platelet count (k/uL). We calculated the PLR by dividing the absolute count of platelets to that of lymphocytes at diagnosis with thorough examination of peripheral blood smears stained with Leishman stain.
- Liver function tests, serum creatinine, serum uric acid, and serum LDH.
- Virology screen (HCV, HBsAg, HIV): HCV Ab was detected using Murex HCV Ag/Ab Combination 4th generation ELISA kit # 4J2453 Anti-Core monoclonal antibody, recombinant antigen and peptides representing the immunodominant regions of NS3 and core. Simultaneously, the Bioelisa ELISA kit was used for detection of Hepatitis B surface antigen (HBsAg). Genscreen™ ULTRA HIV Ag-Ab. The Genscreen™ ULTRA HIV Ag-Ab is a qualitative enzyme immunoassay kit for the detection of HIV p24 antigen and antibodies to HIV-1 (groups M and O) and HIV-2 in human serum or plasma.

2. Work up for CLL diagnosis:

- Microscopic study of bone marrow and peripheral smears.
- Immunophenotyping (IPT) using American (BD FACSCAN-TOII) to diagnose the cases and exclude other types of lymphoma by incubation of washed cells from peripheral blood or bone marrow samples with fluorescein-labelled monoclonal antibody including scoring system of CLL (CD5, CD19,CD23,CD79b,sIgM,CD38), kappa and lambda. Positivity in each marker can be calculated if it is more than 20%.
- FISH for detection of 17p deletion. Interphase FISH technique was conducted on peripheral blood or bone marrow aspiration and trephine. Using the Olympus BX 61, fluorescent microscope. Interphase FISH technique was performed on samples after optimization of the protocol using commercially available probe from Cytocell UK LPH TP53 deletion FISH Probe Kit.

Statistical analysis

Data were analysed on a personal computer running SPSS© for Windows (Statistical Package for Social Scientists) Release 18. A two-tailed p value of >0.05 was considered statistically significant. For descriptive statistics of qualitative variables, the frequency distribution procedure was run with calculation of the number of cases and percentages. For descriptive statistics of quantitative variables, the median and range were used. Association between categorical variables was tested by the Chi Square Test or Fishers exact test. The independent- samples t-test was used to compare the means between two groups. Time to treat was defined as the time from diagnosis until the start of chemotherapy or death. Overall survival was calculated by the Kaplan-Meier Product-Limit Estimator. Comparison of the survival was performed by the Log-Rank Test. Exploring variables for their independent prognostic effect on survival was carried out using the multivariate stepwise Cox's proportional regression hazard model.

Results

The 180 CLL patients were (101 M; 79 F) with mean age 60.27 ± 11.49 years. The incidence of chronic HCV infection and HBV in our study were 38.3% and 3.9% respectively. At diagnosis, the median PLR was 2.5 (range 0.07–42), platelets 138.5 k/µL (range 5–459 k/µL), and the median PDW was 18.5 (range 15.6–24.9). Basic data are illustrated in table I.

Table I. Basic data of studied cases

Character	Value	Percentage
Male/female	101/79	56.1%/43.9%
HCV positive	69	38.3%
HBV positive	7	3.9%
B symptoms – present	107	59%
	Median	**Range**
WBC (k/uL)	61.85	8–960
ALC (k/uL)	52.5	6–900
HB (g/dl)	11	4.3–16.2
Platelet (k/uL)	138.5	5–459
PLR	2.5	0.07–42
PDW	18.5	15.6–24.9
Stage	**Number**	**%**
A	3	1.7%
B	94	52.2%
C	83	46.1%
Prognostic markers		
17p deletion positive (n = 35)	5	14.28%
CD38 positive (n = 93)	33	35.48%
ZAP-70 positive (n = 30)	18	60%
PLR	**Value**	**No (%)**
Low PLR	<2.5	86 (47.8%)
High PLR	≥2.5	94 (52.2%)
PDW		**No (%)**
Low PDW	<18.5 fl	82 (45.6%)
High PDW	≥18.5 fl	98 (54.4%)
Intention to treat – population	**138**	**76.7%**
Treatment protocol	**No**	**%**
Wait and watch	19	10.6%
Purine based	53	29.4%
Alkylators based	108	60%
Status (alive/dead)	115/65	63.9%/36.1%

Low PLR (<2.5) was more frequently observed in male patients (p = 0.06) with stage C (p < 0.001), with 17p deletion (p = 0.017), and CD38 expression (p = 0.08) and intention to treat (p < 0.001), but not with HCV seropositive patients (p = 0.22) and ZAP-70 positivity (p = 0.28) (table II).

High PDW (≥18.5 fl) was more frequently associated with intention to treat population (p = 0.038), and CD38 expression (p = 0.068), but not with 17p deletion (p = 0.25) and seropositive HCV patients (p = 0.43) (table III).

The median time to initiate treatment in CLL patients was 2.05 years. It was found that the majority of intention to treat population was associated with low PLR (p < 0.001), high PDW (p = 0.038), seropositive HCV (p 0.027) and seropostive HBV (p = 0.2).

The median overall survival of the studied group was 5.58 years. CLL patients with stage A, hepatitis C seronegative patients, low PDW, high PLR were associated with superior overall survival with significant value (p = 0.001, 0.017, 0.043, and 0.002 respectively figure 1a, b, c). Multivariate analysis showed that stage A and low PDW were independent factors for OS (p = 0.014 and 0.04 respectively), while high PLR (p = 0.05), and seronegative C (p = 0.1) lost their significance.

Discussion

CLL is considered a heterogeneous disorder associated with different clinical courses which were predicted by staging systems of Binet and Rai. However, these systems do not consider other CLL biological features which can affect the course of the disease [7, 8].

Hitherto, new molecular advances have resulted in the use of expensive and complicated prognostic markers like cytogenetic aberrations (17p deletions, 11q deletions and trisomy 12), β2 micro-globulin, IGHV mutational status, expression of CD38 and ZAP-70 and gene mutations like *NOTCH1*, *MYD88* and *SF3B1* [9].

Unfortunately, most of these biomarkers were not taken in all of our cases because of either the cost and or unavailability. Another limitation to this study would be immune thrombocytopenia. However, to the best of our knowledge,

Table II. Comparison between low PLR and high PLR group in CLL patients

		Low PLR (<2.5)	High PLR (≥2.5)	Test of significance	p
Male		59 (62.76%)	42 (48.84%)	3.53	0.06
Age >65		34 (36.17%)	29 (33.72%)	0.12	0.7
HCV positive		40 (42.55%)	29 (33.72%)	1.48	0.22
HBV positive		4 (4.26%)	3 (3.48%)	0.07	0.54
Stage	A	1 (1.06%)	2 (2.33%)	19.26	<0.001
	B	35 (37.23%)	59 (68.6%)		
	C	58 (58%)	25 (29.06%)		
Intention to treat population		83 (88.29%)	55 (63.95%)	14.87	<0.001
CD38 positive		21 (43.75%)	12 (26.66%)	2.96	0.08
ZAP-70 positive		10 (71.4%)	8 (50%)	1.4	0.28
del (17p)		5 (23.8%)	0 (0%)	5.65	0.017

Table III. Comparison between low PDW and high PDW group in CLL patients

		Low PDW (<18.5 fl)	High PDW (≥18.5 fl)	Test of significance	p
Male		42 (51.2%)	59 (60.2%)	1.46	0.23
Age >65		24 (29.3%)	39 (39.8%)	2.17	0.14
HCV positive		34 (41.5%)	35 (35.7%)	0.62	0.43
HBV positive		4 (4.9%)	3 (3.1%)	0.39	0.53
Stage	A	2 (2.4%)	1 (1%)		
	B	45 (54.9%)	49 (50%)	1.12	0.56
	C	35 (42.7%)	48 (49%)		
Intention to treat population		57 (69.5%)	81 (82.7%)	4.31	0.038
CD38 positive		9 (24.3%)	24 (42.9%)	3.34	0.068
ZAP-70 positive		7 (43.8%)	11 (78.6%)	3.77	0.052
del (17p)		2 (28.6%)	3 (10.7%)	1.45	0.227

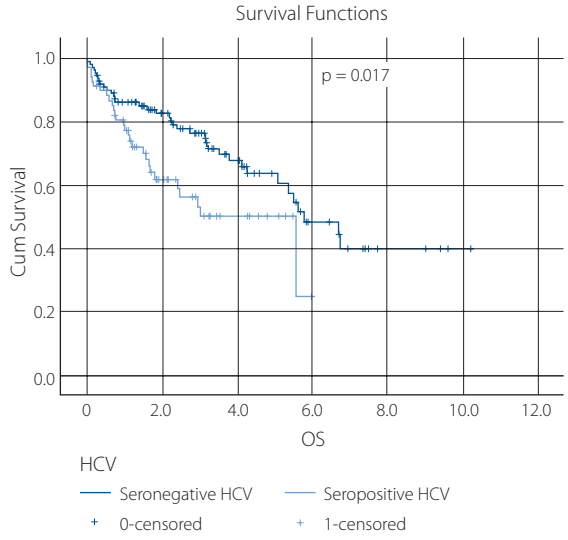

Figure 1a. Effect of HCV infection on overall survival of studied population

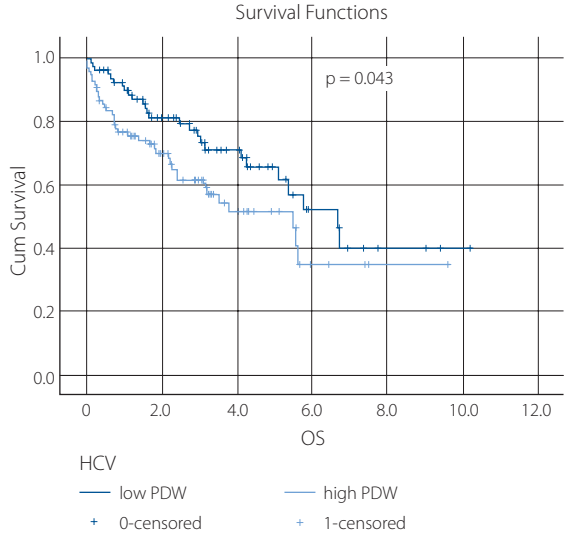

Figure 1b. Effect of PDW on overall survival of studied population

patients with auto-immune hematologic manifestations were not included in this analysis. Only two patients presented

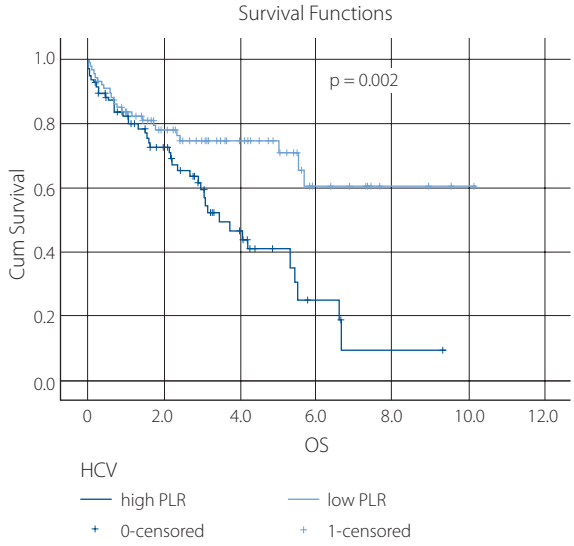

Figure 1c. Effect of PLR on overall survival of studied population

extreme thrombocytopenia and their work up did not reveal an immune phenomenon.

Recently, correlation between cancer and inflammation is an important new area of research. The antitumour activity of inflammation and the associated immune activation, induce tumour growth and progression. Inflammation is an independent predictor for response to therapy, event-free survival and overall survival (OS) in diffuse large B-cell lymphoma (DLBCL) patients [10].

Molica et al. have reported that in newly diagnosed CLL patients, the doubling time of absolute lymphocytic count was an independent predictor of outcomes in those patients [11]. Although platelet count prognostic value in CLL is not well identified, thrombocytopenia is considered a treatment indication [6]. Also, some studies have found that thrombocytopenia results in a compensatory thrombopoietin release which might correlate to some prognostic markers like ZAP-70 and CD38 [12, 13]. So, we used the PLR as it is an easily applicable clinical method that could detect the patients with a poor prognosis early.

Cytopenia in patients with CLL can have multiple causes including progressive bone marrow (BM) infiltration by abnormal lymphocytes, autoimmune disease, therapy-related, non-CLL related disorders, or a combination of these mechanisms [14]. The biological rationale in calculating PLR is that lymphocytosis and thrombocytopenia often occured in the advanced stages of CLL [6].

Our data demonstrated that Low PLR (<2.5) group was significantly associated with poor prognostic markers; stage C ($p < 0.001$), with 17p deletion ($p = 0.017$), and intention to treat ($p < 0.001$). They had significantly shorter OS compared to high PLR ($p = 0.002$) in a univariate analysis, while they lost their significance in multivariate analysis ($p = 0.05$). In solid tumours, a positive relationship between high PLR with worse prognosis for colorectal, gastroesophageal, hepatocellular, pancreatic, and ovarian cancers was identified [15].

Meanwhile, Kang et al. demonstrated that PLR had significant association with a poor prognosis in patients with non-Hodgkin's lymphoma, treated by R-CHOP [16]. Wang et al. reported that high PLR was associated with shorter OS and PFS in patients with DLBCL [10], also Seo et al. found that PLR showed independent significance in patients with advanced stage marginal zone lymphoma treated with rituximab, vincristine, cyclophosphamide, and prednisone protocol [17]. Retrospective analysis of 283 myeloma patients showed that inverse PLR had predictive value for OS and PFS [18].

Despite recent interest in the clinical implications of activated platelets in the setting of cancer, the scope of available data is still limited by the type of malignancy, sample sizes, selected population and clinical outcomes studied. PDW is a measure of platelet heterogeneity caused by heterogeneous demarcation of megakaryocytes. Several cytokines such as IL6, granulocytes colony stimulating factor (G-CSF) and macrophage colony stimulating factor (M-CSF) have dual functions including regulating megakaryopoiesis and tumour progression [19]. Another possible mechanism is that activated platelets create a procoagulant micro-environment that protect the tumour cells from the host immune system [20].

Increased PDW was found in gastric cancer and lung cancer [21, 22], and has been demonstrated to have a poor prognostic impact in melanoma, thyroid cancer, colorectal cancer, and laryngeal cancer. Also, studies, found that an increased PDW was associated with advanced TNM stages and shortened OS in patients with nasopharyngeal cancer. In contrast, other studies showed that decreased PDW was found in thyroid and breast cancer [23, 24], and is an unfavourable predictive factor for non-small cell lung cancer patient survival [25].

To the best of our knowledge, our study is the first to demonstrate the effect of high PDW in CLL patients and it revealed that High PDW (≥18.5 fl) was more frequently associated with intention to treat population ($p = 0.038$), and CD38 expression ($p = 0.068$), but not with 17p deletion ($p = 0.25$) and seropositive HCV patients ($p = 0.4$).

Conclusions

The low PLR and high PDW are associated with poor prognostic markers in CLL patients. CLL staging and PDW are independent predictors of survival. Unfortunately, the other prognostic markers as 17p deletion, CD38 and ZAP-70 were not performed for all our patients. We recommend further prospective studies to evaluate these simple applicable and cheap biomarkers in larger numbers of patients.

Conflict of interest: none declared

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