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Plateletcrit as a prognostic marker in Hodgkin lymphoma: A pilot study

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Ethics Committee Approval
The study was approved by the Ethics Committee of Suleyman Demirel University Faculty of Medicine (dated 11.03.2021 and numbered 137). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Hodgkin lymphoma (HL) is a lymphoproliferative malignancy associated with inflammation. Plateletcrit (PCT) is a mean platelet volume (MPV) and platelet count-derived marker that is useful for evaluating malignancies and inflammatory diseases. International Prognostic Score (IPS-7) and more recently, IPS-3, are two indices indicating the prognosis of patients; however, widespread and easy to interpret prognostic markers are still needed for HL evaluation. Very few studies evaluating the prognostic significance of platelet indices in HL have been published, so we aimed to show the relationship between PCT and other adverse prognostic factors in HL and evaluate whether PCT can be used as a prognostic marker in HL.

Methods: After excluding patients with insufficient data, 75 patients diagnosed with HL and 150 healthy controls were retrospectively analyzed in this case-control study. Evaluation of relationship of PCT and adverse HL prognostic factors, such as age, gender, hemoglobin, leukocytes, lymphocytes (absolute value and percentage), albumin, Ann Arbor stage and B symptoms, IPS-3 and-7 prognostic scores and post-treatment relapse, and progression-free survival of the patients were studied.

Results: Mean MPV values were significantly lower, mean platelet values were significantly higher inpatient group (all $P<0.001$). Patients with high sedimentation had significantly higher mean PCT than those without ($P=0.031$) and a moderately positive correlation between PCT and sedimentation were found ($r=0.33$, $P<0.01$). Mean PCT values after treatment significantly decreased compared to baseline levels ($P<0.001$).

Conclusion: PCT may be useful as a prognostic marker in HL. Further studies were needed to evaluate the relationship between PCT and other prognostic factors, such as IPS-3 and -7.

Keywords: plateletcrit, Hodgkin lymphoma, prognosis

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Introduction

Hodgkin Lymphoma (HL) is a rare lymphoproliferative disease with an incidence of 2 to 3/100000 and a peak incidence of twenty to thirty years [1]. Epstein-Barr virus seems to play a major, although not essential, part in pathogenesis, and viral DNA can be found in substantial proportion of lymph node specimens [2]. The Reed–Sternberg cell, hallmark of the disease, has substantial portions of inflammatory regions compared to malignant ones [3]. These cells are surrounded by large number mature lymphocytes and pro-inflammatory cells showing the inflammatory nature of HL. The disease can be sub-grouped as classic and nodular lymphocyte predominant HL, and 95% of patients are diagnosed as classic HL [4]. Positron emission computed tomography/computed tomography (PET/CT) is generally used for staging and guiding treatment strategies, such as chemotherapy and radiotherapy. Approximately 80% of patients can be cured with a combined modality approach, but only 50% of relapsed patients can achieve long-term success with autologous stem cell transplantation; therefore, research to find different solutions for these patients is ongoing [5]. Programmed death protein 1 (PD-1), a transmembrane protein responsible for T-cell exhaustion and inactivation in peripheral tissues, and cytotoxic T-lymphocyte-associated antigen 4, a T-cell inhibitor found on T cells located in lymph nodes, has attracted much attention since Reed–Sternberg cells also use these pathways to evade immune response [6]. Due to immune mechanisms responsible in the origin and pathogenesis of HL, immune checkpoint inhibitors, such as nivolumab and pembrolizumab, are increasingly used in general practice [7].

Platelets originate from megakaryocytes in the bone marrow and are primarily responsible for the primer stage of hemostasis. In recent years, their role in the immune system has been highlighted asthey release pro-inflammatory cytokines, are responsible for phagocytosis of microbes, mediate leukocyte migration and netosis [8]. Mean platelet volume (MPV) represents the area of platelets in circulation and is associated with platelet activation. Plateletcrit (PCT) is a MPV-bound platelet index and usually associated with inflammatory diseases and cancer [9,10]. Given the inflammatory pathways responsible for HL, the association of platelet indices and HL poses an unanswered question that remains to be determined. Very few studies regarding this issue are available, so in this study, we evaluated whether any relationship between HL, its therapy, and other prognostic factors and PCT exist.

Materials and methods

Two hundred patients diagnosed with HL and treated in our hospital from 2010 to 2020 and 150 healthy controls were retrospectively included in the study. After excluding patients with insufficient data, 75 patients diagnosed with HL and 150 healthy individuals (control group) were retrospectively analyzed. The control group consisted of healthy blood donors who had a complete blood count evaluation before donation. Those who had a diagnosis of chronic inflammatory disease, chronic infection, and/or malignancy in the control group were excluded from the study. In the patient group, the complete blood count at diagnosis and after therapy was recorded, and PCT was calculated. First, whether MPV and PCT differed significantly in patient group was checked after which the evaluation of the relationship between PCT and age, gender, hemoglobin, leukocytes, lymphocytes (absolute value and percentage), albumin, Ann Arbor stage and B symptoms, IPS-3 and -7 prognostic scores, post-treatment relapse, and progression-free survival of the patients was determined. Progression-free and overall survival results were recorded as months.

Statistics analysis

Statistics analyses were performed using a package program. Descriptive statistics were represented as number, percentage, mean, and standard deviation. Conformity of continuous variables to normal distribution was examined. Student's t-Test was used for the comparison of normally distributed variables in two independent groups, and the Mann_Whitney U Test was used for non-normally distributed variables. A Kruskal–Wallis multiple comparison test was used to compare more than two independent groups that did not fit normal distribution. The difference in frequency between the groups was compared using the chi-squared test. Dependent group Student's t-Test was used for comparisons of measurements with pairwise times. The relationship between the variables was determined by Pearson's correlation analysis. In multivariate analyses, the independent effects of possible factors (variables associated with univariate analysis and close to the type 1 error level [cut-off value P=0.25]) on PCT were examined using a linear regression model. The variance inflation factor (VIF) values were examined for the multicollinearity problem among the independent variables. Those above VIF 3 were not included in the model. The "enter" method was used for linear regression analysis. The model fit was examined using the required residual and fit statistics.

The approval of the Ethics Committee of Suleyman Demirel University Faculty of Medicine dated 11.03.2021 and numbered 137 were obtained for the study. Informed consent was obtained from all the participants, and all study steps were performed in accordance with Declaration of Helsinki.

Results

The mean age of Hodgkin patients at diagnosis was 51.1 (17.8; min 20–max 86), while the mean age of the control group was 48.3 (10.3; min 20–max 66). In the first phase of the study, patients and those in the control group were compared, and the results are presented in Table 1. No differences between the HL group and the controls in terms of age and gender were found (P=0.214 and P=0.100, respectively). Compared to the control group, mean MPV values were found to be significantly lower and PLT mean values were found to be significantly higher in the HL group (P<0.001and P=0.001, respectively). Although the mean PCT values in the HL group were higher than the control group, this difference was not statistically significant (P=0.107, Table 1).

PCT values of patients at diagnosis and the factors affecting this value were examined in univariate and multivariate analyses (Table 2). No significant differences were found with PCT according to age, gender, presence of B symptoms, Ann-Arbor stage, relapse status, IPS-3 and -7 scores, subtypes, presence of bulky lesions, chemotherapy, and total and

progression-free survival of patients. It was found that patients with sedimentation counts higher than 50 mm/h had significantly higher mean PCT than those without (P=0.031). In the linear regression model, each unit increase in sedimentation count caused a significant increase in the PCT value by 0.001 units (P=0.003, Table 2).

Table 1: Differences between Hodgkin lymphoma and control group

Characteristics	HL	Control group	*P*-value
Age*	51.1 (17.8)	48.3 (10.3)	0.214
Gender**			
Women n (%)	28 (37.3%)	40 (26.7%)	0.100
Men n (%)	47 (62.7%)	110 (73.3%)	
PCT*	0.217 (0.08)	0.202 (0.03)	0.107
MPV*	7.8 (1.0)	8.4 (0.8)	<0.001
PLT*	293.2 (120.9)	242.9 (47.4)	0.001

* independent groups T-test, ** Chi-square test, PCT: Plateletcrit, MPV: Mean Platelet Volume, PLT: Platelet, HL: Hodgkin Lymphoma

Table 2: Factors Associated with plateletcrit counts in patients with HL

Characteristic		n	Single analysis		Multiple analysis ¥	
			Mean (SD)	*P*-value	B (95% CL)	*P*-value
Age µ	50≤	37	0.205(0.07)	0.172	0.001(0.000-0.001)	0.233
	50>	38	0.230(0.09)			
Gender µµ	Woman	28	0.209(0.08)	0.472		
	Man	47	0.223(0.08)			
B Symptom µ	Available	30	0.214(0.09)	0.755		
	None	45	0.220(0.07)			
Ann-arbor*	1	3	0.246(0.06)	0.284		
	2	31	0.218(0.06)			
	3	29	0.230(0.08)			
	4	12	0.179(0.11)			
Relapse µµ	Available	13	0.211(0.10)	0.955		
	None	62	0.219(0.08)			
Ips3 *	0	23	0.221(0.06)	0.192	-0.02(-0.044-0.004)	0.094
	1	34	0.217(0.08)			
	2	11	0.249(0.10)			
	3	7	0.158(0.10)			
Ips7 *	0	8	0.230(0.05)	0.091		
	1	18	0.202(0.07)			
	2	18	0.213(0.05)			
	3	15	0.216(0.09)			
	4	12	0.233(0.11)			
	5	2	0.377(0.07)			
	6	2	0.112(0.02)			
Subtype*	Classical HL	16	0.217(0.10)	0.300		
	Lymphocyte Predominant	6	0.216(0.06)			
	Mix cellular	25	0.226(0.07)			
	Nodular sclerosan	22	0.225(0.08)			
	Lymphocyte rich	5	0.169(0.04)			
	Lymphocyte depleted	1	0.098(0.00)			
Bulky lesion µµ	Available	5	0.206(0.10)	0.705		
	None	70	0.219(0.08)			
Sedim µµ	50≤	44	0.203(0.06)	0.031	0.001(0.00–0.001)	0.003
	50>	31	0.238(0.10)			
PFS *	50≤	39	0.209(0.09)	0.544		
	51-100	16	0.221(0.07)			
	101-150	14	0.224(0.09)			
	150>	6	0.252(0.04)			
OS *	50≤	31	0.209(0.08)	0.210	0.00(0.000–0.001)	0.231
	51-100	20	0.211(0.09)			
	101-150	16	0.220(0.08)			
	150>	8	0.263(0.04)			
CT *	ABVD	65	0.212(0.08)	0.794		
	BEACOOP	8	0.221(0.11)			
	DHAP	2	0.218(0.18)			
Total		75	0.218(0.08)			

Data were presented as mean (standard deviation). µ independent groups T test, µµ Mann–Whitney U test, *Kruskal–Wallis test, ¥ model fit values for multiple regression analysis. (R=0.422; R Square=0.178; Adjusted R Square=0.131; Durbin–Watson=1.910). PFS: Progression free survival, OS: Overall survival, CT: Chemotherapy, Sedim: Sedimentation, ABVD: Adriamycin–Bleomycin–Vinblastine–Dacarbazine, BEACOPP: Bleomycin–Etoposide–Adriamycin–Cyclophosphamide–Oncovin–Procarbazine–Prednisone, DHAP: Dexamethasone, high dose Cytarabine–Cisplatin, PCT: plateletcrit: IPS: International Prognostic Score

Correlations between the mean PCT value of patients and their variables were examined. A moderately negative correlation (r=–0.38) between PCT and MPV values of patients was found, and a moderately positive correlation between PCT and sedimentation was also found (r=0.33; P<0.01, Table 3).

The mean PCT value of male patients was 0.223 (0.08) at diagnosis and PCT significantly decreased to 0.172 (0.06; P<0.001) after chemotherapy. An insignificant decrease was found in female patients after treatment (P=0.226). When all patients were evaluated together, mean PCT values at diagnosis and after chemotherapy were 0.218 (0.08) and 0.177 (0.07), respectively, and this decrease was also significant (P<0.001).

Table 3: Correlation of PCT Counts and Other Variables in HL Patients

Characteristic	PCT (r)
Age (r)	0.07
MPV (r)	-0.38**
PFS (r)	0.21
OS (r)	0.22
SEDIM (r)	0.33**

**P<0.01, r: Pearson correlation coefficient, PCT: Plateletcrit, MPV: Mean Platelet Volume, PFS: Progression free survival, OS: Overall survival, SEDIM: Sedimentation

Discussion

IPS-3 and -7 are new scoring systems for evaluating the prognosis of HL. The IPS-7 score incorporates age, gender, albumin count, hemoglobin, white blood cell count and lymphopenia and highlights prognosis at diagnosis. Recently, it was shown that the IPS-3 score (age, hemoglobin >10.5 g/dl, and stage) defined comparable results to those defined in IPS-7 [11]. It is necessary to evaluate new and easily available prognostic factors, such as IPS-3. In our study, mean platelet count was significantly higher and mean MPV value was significantly lower in HL patients. Increased platelet counts could be attributable to malignancy, which is an etiological factor that is associated with secondary thrombocytosis. Karagoz et al. [12] has shown an increase in platelet counts compared to controls in colon malignancy occurs. Decreased MPV can be seen in a variety of diseases, such as inflammatory bowel diseases, systemic lupus erythematosus, and neoplasm [13]. Decreased MPV values were found in lung and cervical cancer in which a pre-operative low MPV count was considered an adverse prognostic factor [14,15]. Only one study evaluating the prognostic status of MPV in HL has been published. While MPV was not used as a prognostic marker in this study, mean MPV was significantly lower in patients with venous thromboembolism compared to those without [16].

Platelet counts were also elevated significantly in the patient group compared to controls. Platelets were found to be elevated in a variety of cancers and high platelet count was associated with metastatic disease and poor prognosis [17]. Thrombocytosis was found to be a common finding in lymphomas [18]. We also found significantly higher mean platelet values in HL patients in agreement with studies in the literature.

High PCT was found to be an adverse prognostic factor in non-small cell lung cancer [10]. Also, high PCT levels were significantly associated with tumor stage, size, and vascular invasion in colorectal carcinoma [19]. We found that mean PCT was higher in patients compared to control group even though the difference was insignificant. This finding could be attributed to two reasons. First, mean platelet count was higher and mean MPV was lower in the HL group. PCT is associated with both variables, so this association could be the reason for insignificant high PCT value. Second, our study group has a low number of

patients compared to other studies. With a much larger study group, PCT might also be significantly affected.

In this study, whether PCT could be a prognostic factor for HL was evaluated, and it was shown that only high sedimentation rate (> 50 mm/h) was associated with significantly elevated PCT. Elevated erythrocyte sedimentation rate has been shown to be an adverse prognostic factor for HL, and our results were consistent with those in the literature [20]. A significant positive correlation with each unit of sedimentation elevation and PCT was found. Also, when all study groups were analyzed, PCT levels declined significantly after chemotherapy. Besides the relationship with elevated sedimentation rate, we could not find any relationship between PCT and other adverse prognostic factors.

Only a few studies evaluating the prognostic status of platelet-derived factors in HL have been published. Tao et al. reported that low platelet/platelet distribution width and high platelet/lymphocyte ratio were adverse prognostic factors in patients with newly diagnosed advanced stage HL [21]. In early stages, pre-treatment neutrophil/lymphocyte and platelet/lymphocyte ratios were found to be significant factors related to progression in HL [22]. Rupa-Matysek et al. [16] evaluated the prognostic significance of MPV in HL and found high platelet and low MPV levels in HL compared to the control group, and while MPV could not be used as a prognostic marker, it could a useful tool for predicting thrombosis in HL. We also found low MPV and high platelet counts in patients with HL.

Limitations

Some drawbacks in this study should be mentioned. The number of patients in our study group was small compared to other studies evaluating the prognostic status platelet indices; in addition, the study was not a prospective one. These two drawbacks could be major factors affecting our research results. With much larger study groups as in literature, we might reach more robust conclusions about other adverse prognostic factors and PCT. However,, to our best knowledge, our study is the first in its field to evaluate the prognostic status of PCT in HL, so it should add some useful and new information to the literature.

Conclusion

For the first time in the literature, this study showed that high PCT values are associated with high sedimentation rate, and treatment leads to a significant reduction PCT counts, so PCT could be used as a prognostic marker in HL. Studies with much larger patient groups should be arranged to evaluate the prognostic significance of PCT with other adverse prognostic factors, such as IPS-3 and -7 in HL.

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