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Research

Are Platelet-related Parameters Predictive of the Prognosis of Hodgkin's Lymphoma?

Hodgkin Lenfoma Prognozunda Platelet İlişkili Parameterler Prediktif Midir?

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ABSTRACT

Objective: Hodgkin's lymphoma has a good prognosis unless it has relapsed or become refractory. The predictive value of platelet (Plt)-related parameters, namely, mean Plt volume (MPV), plateletcrit (PCT), Plt distribution width, and Plt, is shown in some solid tumors and hematological malignancies, but it remains unknown in Hodgkin's lymphoma. This study aimed to define their values and effects on staging and relapsing status in patients with Hodgkin's lymphoma by comparing them with those in healthy subjects.

Methods: Values of Plt-related parameters of 217 patients with Hodgkin's lymphoma and 205 healthy individuals were documented and compared according to the disease stage and relapsing status. We defined the cutoff values for diagnosis, staging, and relapsing status of these parameters using the receiving operating characteristic curve analysis.

Results: For diagnosis, the cutoff values of MPV, Plt, and PCT were 8.49 fL, 32,1000/mm^3, and 0.31, respectively. For staging, the cutoff values of MPV and Plt were 9.5 fL and 12 fL, respectively. None of the parameters were associated with relapsing status.

Conclusion: This is the first study evaluating Plt-related parameters in Hodgkin's lymphoma. Further studies including survival analyses will clarify the effect of these parameters on Hodgkin's lymphoma.

Keywords: Hodgkin's lymphoma, platelet, MPV, PCT, PDW

ÖZ

Amaç: Hodgkin lenfoma nüks etmedikçe veya refrakter olmadıkça iyi prognoza sahiptir. Trombosit ilişkili parameterlerin (MPV, PCT, PDW, Plt) prediktif değeri bazı solid tümörlerde ve hematolojik malignitelerde gösterilmiştir, ancak Hodgkin lenfomada halen bilinmemektedir. Biz de çalışmamızda Hodgkin lenfomalı hastalarla sağlıklı bireylerde bu parameterlerin düzeylerini karşılaştırarak tanısal değerleri ile evreleme ve nüks durumu üzerindeki etkilerini tanımlamayı amaçladık.

Gereç ve Yöntem: Two hundred seventeen Hodgkin lenfoma hastası ve 205 sağlıklı bireyin trombosit ile ilgili parameterleri incelendi ve karşılaştırıldı. Hastaların değerleri tanı, evre ve nüks durumuna göre karşılaştırıldı. Alım çalışma karakteristik eğrisi analizi ile tanı, evre ve nüks durumu için parameterlerin cutoff değerlerini tanımlamayı planladık.

Bulgular: MPV, Plt ve PCT'nin tanıda kesim değeri sırasıyla 8,49fL, 32.1000/mm^3, 0,31 idi. MPV ve Plt'nin de evrelemede cutoff değeri sırasıyla 9,5fL, 12fL bulundu. Hiçbir parameter nüks ile ilişkili bulunmadı.

Sonuç: Bu, Hodgkin lenfomada trombosit ile ilişkili parameterleri değerlendiren ilk çalışmadır. Sağkalım analizlerini içeren ileri çalışmalar, bu parameterlerin Hodgkin lenfoma üzerindeki etkisini netleştirecektir.

Anahtar Kelimeler: Hodgkin lenfoma, platelet, MPV, PCT, PDW

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INTRODUCTION

Hodgkin's lymphoma (HL) is malignant lymphoid neoplasia with symptoms such as lymphadenopathy, constitutional symptoms, itching, and fatigue upon diagnosis that histologically presents as Reed-Sternberg/Hodgkin cells in the center surrounded by non-neoplastic inflammatory cells. HL has two subtypes: the classical type that constitutes 90% of the cases, and the nodular lymphocyte predominant type that constitutes 10% of the cases. While the classical type has two peak periods, as young adults and older adults, the nodular lymphocyte predominant type is more common in children and in adults in their 40s and 50s (1,2). They are staged according to the Lugano classification, and the treatment is planned according to their early/advanced stage and risk status. Old age, advanced stage, high erythrocyte sedimentation rate, B symptoms, high number of involved lymph nodes, presence of bulky or mediastinal mass, male sex, and leukocytosis (>15,000/mm^3), and lymphopenia (<8% of leukocyte count or absolute lymphocyte count <600/mm^3) are poor prognostic criteria. The treatment is usually curative, and 5-year survival of ≥90% is observed. Response to treatment is usually assessed by imaging methods based on the reduction in tumor mass. However, the prognosis is poor in primary refractory or early relapsed cases. Therefore, in these patients, it is necessary to consider autologous bone marrow transplantation after salvage chemotherapy (3).

Platelets (Plt) are activated by thrombin released by the tumor, and they contribute to tumor formation and propagation by causing the release of angiogenic factors such as Plt-derived growth factor and vascular endothelial growth factor (4). In addition, activated Plts protect tumor cells from lysis (5). Plt-related factors present the characteristic properties (size and activity) of Plts, namely, mean Plt volume (MPV), Plt distribution width (PDW), and plateletcrit (PCT). These parameters are thought to be related to tumor metastases and therefore have predictive value in the prognosis of many tumors such as colon, lung, cervical, and gastric cancers and diffuse large B-cell lymphomas (6-9). Sabrkhany reported that Plt-related parameters could be used in the early diagnosis of early-stage cancer, and in their meta-analyses, Zhang showed that high Plt counts were associated with a poor prognosis in lung cancers (10,11). In another study, Plt >400,000/mm^3 was reported to be a prognostic indicator (12). Conversely, Lopes et al. (13) reported that high pretreatment Plt counts had no predictive value.

MPV refers to the Plt volume and is an early marker of Plt activation. Since MPV decreases as a result of the consumption of large Plts in inflammatory events, it is considered an inflammatory marker. In addition, MPV has been reported to be elevated in myocardial infarction, unstable angina, and stroke (14). This result is probably related to the fact that large Plts cause acute coronary syndrome more frequently. By contrast, in a meta-analysis of 38 studies, Chen et al. (15) reported that MPV had no prognostic value in malignancies. Another study showed that a low MPV reduced overall survival in multiple myeloma (16).

PCT is calculated using the formula MPV × PLT/10 and represents the total Plt volume. Its poor prognostic effect was reported in pancreatic cancers (17). In another study, the PCT value was found to be higher in patients with metastatic lung cancer than in those without metastasis (18).

PDW shows the variation in Plt size. Its increase indicates intense active thrombocyte production. Unlike other Plt-related parameters, the current literature data reveal conflicting results about its prognostic value in solid cancers. Some studies have declared that it is a prognostic factor and plays a role in metastasis, while some have denied these theories (19,20). Hirahara et al. (21) reported no relationship between prognosis and PDW in esophageal cancers.

To the best of our current knowledge, no study has compared Plt-related parameters in healthy populations with patients with HL. Thus, this study aimed to understand whether Plt-related parameters in HL are different from those in healthy populations and affect staging and relapsing status in HL.

METHODS

Local Ethics Committee Approval was obtained from Mersin University (no. 2020/42). Records of 217 patients (aged 18-70 years) histopathologically diagnosed with HL in three centers between January 2000 and December 2020 were retrospectively examined. Demographic data, histological subtypes, stages, MPV, PCT, PDW, and Plt valuesof all patients at the time of diagnosis were recorded. Data of 205 Plt donors who applied to the apheresis unit in one of these centers and were identified as the control (healthy) group and had no malignancy or inflammatory disease at the same interval were also documented. The Chi-squared test was used to examine whether Plt-related factors differ between the patient and control groups, and the Kaplan-Meier method was used to examine whether Plt-related factors were effective on prognosis. We also tried to define the cutoff values of the parameters for diagnosis, stage, and relapsing status using receiving operating characteristic (ROC) curve analysis.

RESULTS

Data of 205 individuals in the control group and 217 patients in the HL group were documented. The mean ages between the two groups were comparable (36.7 and 38.9 years, respectively). Male predominance was more common in both the control and HL groups (95.6% and 64.5%, respectively). The median follow-up time was 58 months. The adriamycin + bleomycin + vinblastine + dacarbazine protocol was the most used treatment protocol (n=118). Overall, histopathological data of 184 patients were obtained. The most common histopathological type was a nodular sclerosing type (n=86). Other types were mixed cellular form (n=67), lymphocyte-rich (n=21), HL + non-HL (n=5), and not otherwise specifed (n=5). Information about the disease stage could be obtained in 185 patients, of which 68 were in the early-stage and 117 were in the advanced stage. The median follow-up time was 68 and 51 months, respectively. Demographic data are summarized in Table 1.

In total, the PDW value was obtained in 54 patients. They were classified according to their staging and relapsing status, except for one patient. The median PDW value was not significantly different in the control and HL groups, early-stage and advanced stage groups, and relapsed and non-relapsed groups (p=0.250, p=0.919, and p=0.936, respectively) (Table 2).

The MPV was significantly higher in the control group than in the HL group (9.7 vs 8.8 fL, p<0.001). It is also higher in the early-stage group than in the advanced stage group (8.9 fL vs 8.4 fL, p=0.033). The mean Plt count was higher in the HL group than in the control group (p<0.001). It was also higher in the advanced stage group than in the early-stage group (p=0.033). While the mean PCT value was lower in the control group than in the HL group, it was not significantly different in patients with early- and advanced stage disease. Values of MPV, Plt, and PCT at the time of diagnosis are summarized in Tables 3,4.

In total, data of 182 patients were evaluated for relapsing status. None of the values of MPV, Plt, and PCT showed a significant difference in terms of relapsing status (Table 5).

Whether the parameters had a diagnostic value was assessed by the ROC curve analysis (Table 6) (Figure 1). Accordingly, the diagnostic cutoff values of MPV and Plt were 8.49 fL and 321,000/mm³, respectively. No significant difference was found between the diagnostic power of MPV and Plt, but both of them were higher than of PCT.

Whether the parameters had a cutoff value for the early and advanced stages were assessed with the ROC curve analysis (Figure 2) (Table 7). The cutoff values of PDW and PCT to determine staging were not defined. To determine advanced disease stages, the cutoff values of MPV and Plt were >9.5 fL and 388,000/mm³, respectively [area under curve (AUC): 0.59, p=0.038 and AUC: 0.60, p=0.0179, respectively]. No difference was found when the predictive power of Plt and MPV values on staging was compared.

Table 1. Demographic data

	HL group	Control group
Number of patients (n)	217	205
Mean age (years)	38.9	36.7
Male/female ratio	64.5	95.6%
Median follow-up time (months)	58	-
Histological subtypes (n)		
nodular sclerosing	86	-
mixed cellular	67	-
lymphocyte-rich	21	-
HL + NHL	5	-
not otherwise specifed	5	-
Stage early	68	-
advanced	117	-

HL: Hodgkin's lymphoma, NHL: Non-Hodgkin's lymphoma

Table 2. Comparison of PDW value between the control and patient groups, early and advanced stage groups, and non-relapsed and relapsed groups

	Control group n=205		HL group n=54		
PDW (fL)	**Median**	**Q1-Q3**	**Median**	**Q1-Q3**	**p**
	12.4	11-16.10	12	10.35-15.55	0.250
	Early-stage n=19		Advanced stage n=34		
PDW (fL)	Median	Q1-Q3	Median	Q1-Q3	p
	13	10-16	12	10.4-15.28	0.919
	Non-relapsed n=44		Relapsed n=7		
PDW (fL)	mean	s. deviation	mean	s. deviation	p
	13.4	5,43923	13,2714	2,85524	0.936

PDW: Platelet distribution width, PCT: Plateletcrit, MPV: Mean platelet volume, HL: Hodgkin's lymphoma

DISCUSSION

Many studies have shown that Plt-related parameters were prognostic factors and affected overall survival and progression-free survival in many solid-organ cancers and some hematological malignancies such as multiple myeloma

Table 3. Comparison of MPV, Plt, and PCT values between the control and HL groups

	Control group n=205		HL group n=217		
	mean	Standard deviation	mean	Standard deviation	p
MPV(fL)	9.7293	1.16544	8.8432	1.60144	**<0.001**
Plt (1/mm³)	258756.098	43601.6844	319468.203	125302.2311	**<0.001**
PCT	.252585	.0557537	.275647	.1019611	0.004

PDW: Platelet distribution width, PCT: Plateletcrit, MPV: Mean platelet volume, HL: Hodgkin's lymphoma

Table 4. Comparison of MPV, Plt, and PCT values between the early and advanced stage

	Early-stage n=68		Advanced stage n=117		
	mean	S. deviation	mean	S. deviation	p
MPV(fL)	8.9461	1.66652	8.4364	1.50478	0.033
Plt (1/mm³)	299360.870	114087.6936	341294.068	136682.1025	0.033
PCT	.262196	.0946792	.281737	.1114290	0.224

PDW: Platelet distribution width, PCT: Plateletcrit, MPV: Mean platelet volume

Table 5. Comparison of MPV, Plt, and PCT values between the non-relapsed and relapsed groups

	Non-relapsed n=148		Relapsed n=34		
	mean	Standard deviation	mean	Standard deviation	p
MPV(fL)	8.7114	1.60248	8.1876	1.38796	0.080
Plt (1/mm³)	321081.757	128370.7466	336602.941	142043.7288	0.534
PCT	.272977	.1045213	.270844	.1136776	0.916

PDW: Platelet distribution width, PCT: Plateletcrit, MPV: Mean platelet volume

Table 6. ROC curve analyses for diagnosis

Parameter	AUC (CI)	p	cutoff	Specificity (C)	Specificity (C)
MPV (fL)	0.690 (0.644-0.734)	<0.001	≤8.49	47 (40.2-53.9)	87.80 (82.5-92)
PDW (fL)	0.551 (0.488-0.613)	0.3105	≤10.7	33.96 (21.5-48.3)	88.29 (83.1-92.4)
Plt (1/mm³)	0.653 (0.606-0.699)	<0.001	>321,000	47.47 (40.7-54.3)	90.24 (85.3-93.9)
PCT	0.559 (0.511-0.607)	0.0379	>0.31	34.10 (27.8-40.8)	89.76 (84.8-93.5)

PDW: Platelet distribution width, PCT: Plateletcrit, MPV: Mean platelet volüme, ROC: Receiver operating characteristic, AUC: Area under curve, CI: Confidence interval

and diffuse large B-cell lymphoma. Plts protect tumor cells from lysis, and they are responsible for tumor invasion and metastasis and thrombosis formation by activating nuclear factor-kB and tumor growth factor B/Smad pathways (22,23).

In a previous study, high Plt counts were shown to be associated with a poor prognosis in cancers (24). In the present study, the mean Plt count was higher in patients with HL than in healthy individuals, similar with reports about most cancers. In another study, high Plt counts were shown to be a messenger in early-stage cancers; similarly, it can be speculated that the cutoff Plt count >321,000/mm³ is predictive for the diagnosis of HL (25). Moreover, patients with Plt count >388,000/mm³ was considered to have advanced diseases according to the ROC analysis. Based on this, Plt count >388,000/mm³ can be considered a poor prognostic criterion.

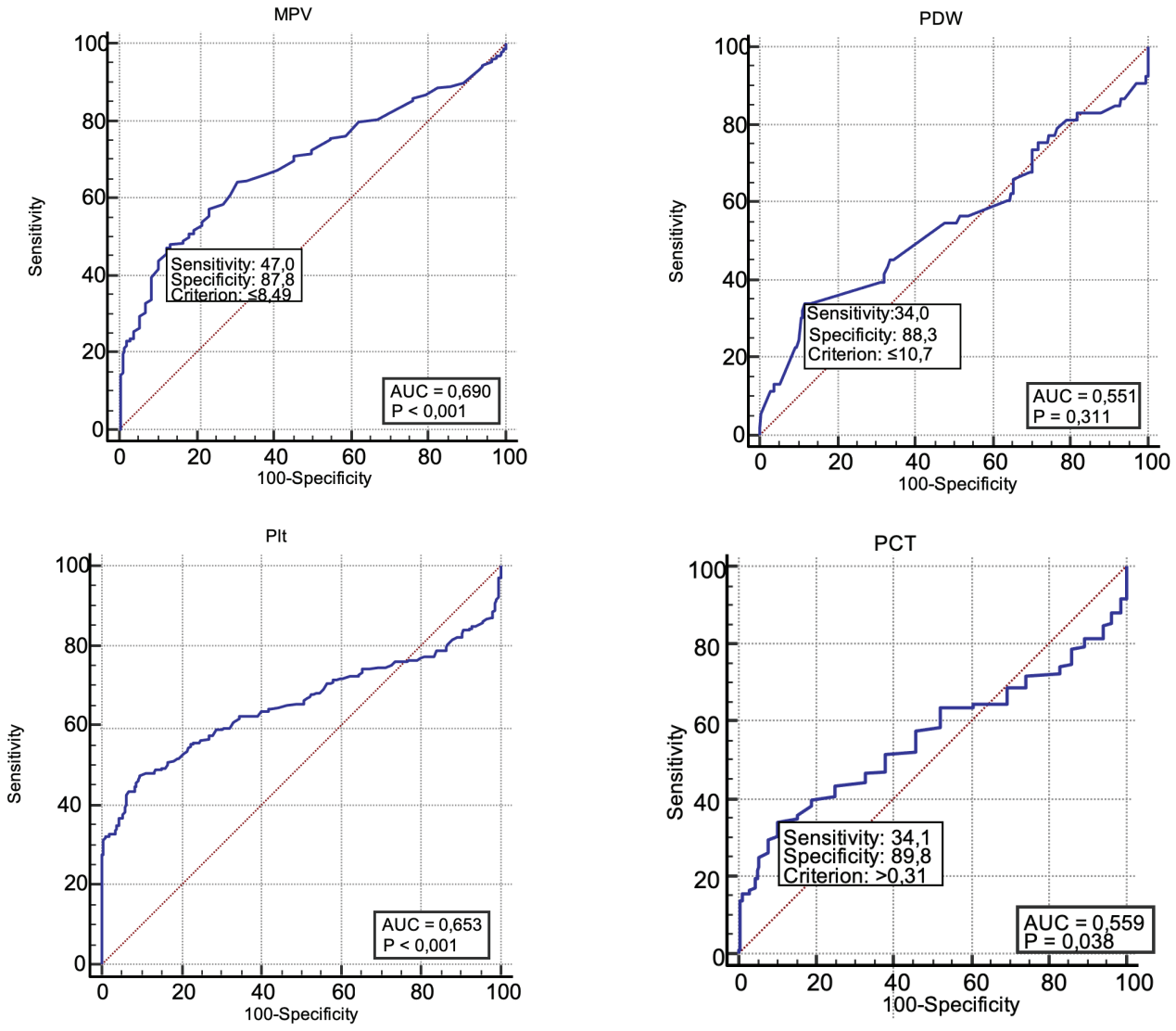

Figure 1. Receiver operating characteristic curve analyses for diagnosis
PDW: Platelet distribution width, PCT: Plateletcrit, MPV: Mean platelet volüme, ROC: Receiver operating characteristic, AUC: Area under curve, CI: Confidence interval

The MPV value at diagnosis is higher in patients with diabetes mellitus, hypercholesterolemia and metabolic syndrome, and smoking status than in the normal population. High MPV values are associated with atherosclerosis, stroke, and myocardial infarction (26-28). However, the prognosis worsened as the MPV value decreased in patients with cancer. In resectable colon, breast, cervical, renal cell, and lung cancers, diffuse large B-cell lymphoma, and multiple myeloma due to hematological malignancies, low MPV values have been associated with a poor prognosis (6-8, 29-32). In chronic lymphocytic leukemia, those with low MPV values received treatment more frequently and needed initial treatment earlier, with the coexistence of other poor prognostic factors (33). However, MPV was reported to have no prognostic value in malignancies in a meta-analysis (15). In our study, MPV was significantly lower in the HL group than in the control group (8.8 fL vs 9.7 fL), in line with literature data. It was also significantly lower in advanced stage than in early-stage cases (8.4 fL vs 8.9 fL). The diagnostic value of MPV was determined as ≤ 8.49 fL, which was lower than those in the studies for CLL (10.4 fL) and DBBHL (9.1 fL), but similar to that in multiple myeloma (8.5 fL) (9,16, 33). For staging, the cutoff value of MPV was 9.5 fL. Therefore, MPV <9.5 fL may be associated with a poor prognosis. By contrast, MPV was not a strong indicator of relapse.

PCT was reported to have a poor prognostic value in pancreatic and resectable lung cancers and was higher in

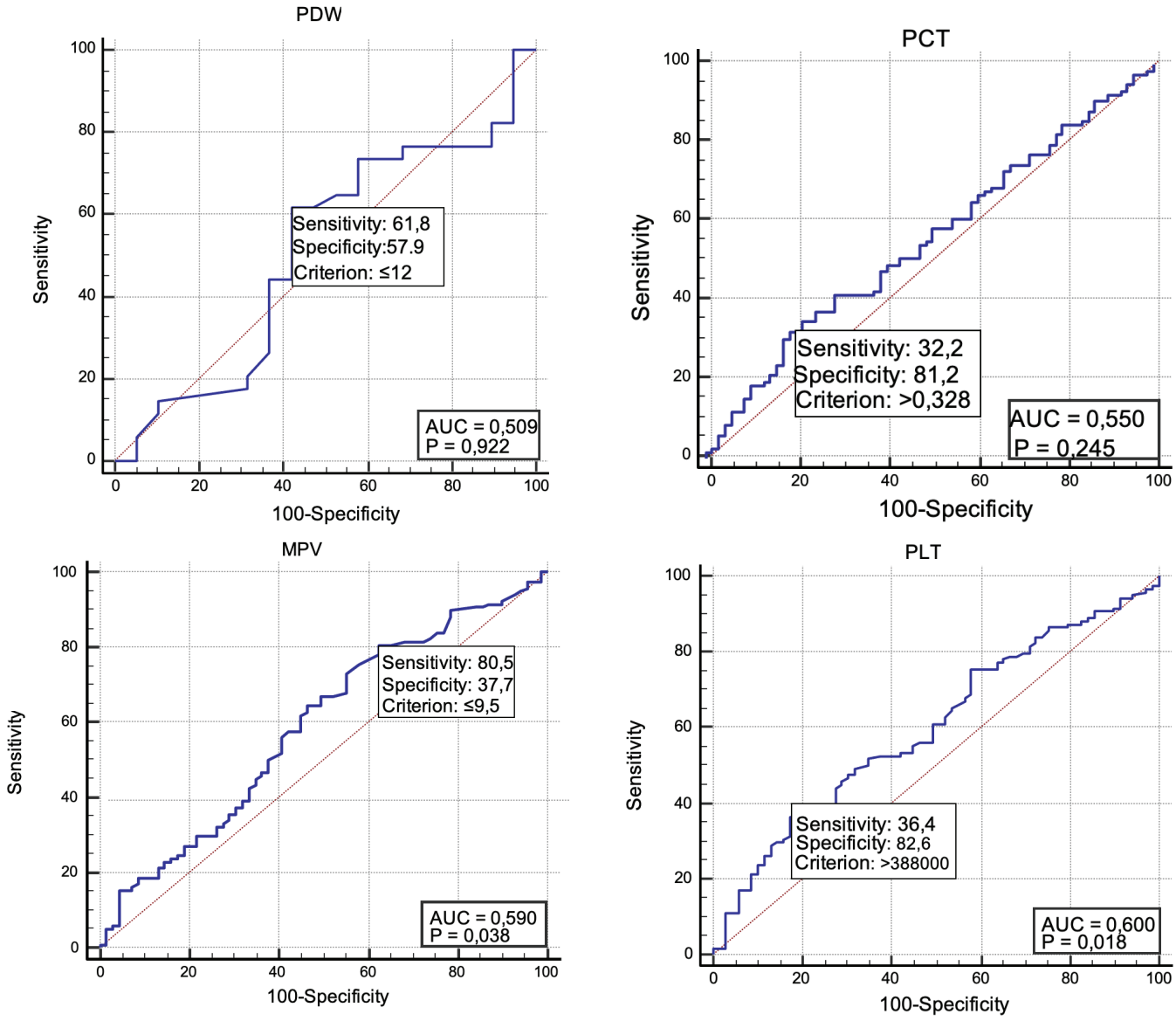

Figure 2. Receiver operating characteristic curve analyses for staging
PDW: Platelet distribution width, PCT: Plateletcrit, MPV: Mean platelet volüme, ROC: Receiver operating characteristic, AUC: Area under curve, CI: Confidence interval

Table 7. ROC curve analyses for staging

Parameter	AUC (CI)	p	cutoff	Sensitivity (CI)	Specificity (CI)
MPV (fL)	0.590 (0.516-0.662)	0.0380	≤9.5	80.51 (72.2-87.2)	37.68 (26.3-50.2)
PDW (fL)	0.509 (0.368-0.649)	0.9222	≤12	61.76 (43.6-77.8)	57.89 (33.5-79.7)
Plt (1/mm³)	0.600 (0.526-0.671)	0.0179	>388,000	36.44 (27.8-45.8)	82.61 (71.6-90.7)
PCT	0.550 (0.476-0.623)	0.2453	>0.328	15.25 (9.3-23)	89.86 (80.2-95.8)

PDW: Platelet distribution width, PCT: Plateletcrit, MPV: Mean platelet volüme, ROC: Receiver operating characteristic, AUC: Area under curve, CI: Confidence interval

patients with metastatic lung cancer than in those without metastatic ones (6,17,18). In this study, the PCT value was significantly higher in the HL group than in the control group. The cutoff PCT value was identified for diagnosis, but not for staging and relapsing status. Therefore, we could not consider PCT as a prognostic factor for HL.

Current literature data examining the prognostic value of PDW in solid cancers provide conflicting results (19-21). In the present study, no significant difference was found between the HL and control groups and between the early and advanced stages. Thus, PDW may not be a marker of either diagnosis or prognosis.

In this study, we found that PLT, MPV, and PCT have diagnostic values for HL. When the determinative powers of these parameters were compared, no significant difference was found. By contrast, Plt and MPV were found to have a strong effect, but PDW and PCT did not affect staging. When the determinative powers of Plt and MPV were compared, no significant difference was found.

Study Limitations

This study has some limitations. First, the relation of Plt-related factors with survival was not analyzed, and their prognostic values were evaluated based on the stage. Second, because the follow-up times of patients were very short and we could not perform survival analysis, we avoid defining the cutoff values for Plt-related parameters to determine relapsing status. Third, we could not reach the full data of all patients. Fourth, examining the relationships between Plt-related factors and other prognostic factors such as erythrocyte sedimentation rate, B symptoms, number of involved lymph nodes, presence of large mass, presence of mediastinal mass, gender, leukocytosis, and lymphopenia could have strengthened our study.

CONCLUSION

Following our literature reviews, our study is the first to evaluate the comparison of Plt-related parameters in patients with HL and healthy populations. As mentioned above, when examined together with the survival analysis and other variables, the prognostic value of these parameters will become more evident.

ETHICS

Ethics Committee Approval: Local Ethics Committee Approval was obtained from Mersin University (no. 2020/42).

Informed Consent: Retrospectively study.

Authorship Contributions

Surgical and Medical Practices: A.A., Ö.M., V.K., S.Ü., K.A., Concept: Ö.M., V.K., Design: AA., V.K., G.Ö.T., A.T., E.N.T., Data Collection or Processing: A.A., Ö.M., V.K., S.Ü., K.A., Analysis or Interpretation: G.Ö.T., A.T., E.N.T., Literature Search: A.A., V.K., E.N.T., Writing: AA., V.K., E.N.T.

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