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Does Delta Hemoglobin-Albumin-Lymphocyte Platelet (HALP) Score Predict the Risk of Early Progression in Patients Treated with CDK4/6 Inhibitors?

Delta Hemoglobin-Albümin-Lenfosit-Trombosit (HALP) Skoru Metastatik Meme Kanserinde CDK4/6 İnhitibitörü ile Erken Progresyon Riskini Predikte Eder mi?

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ABSTRACT

Aim: This study aims to determine the predictive value of dynamic change in hemoglobin-albumin-lymphocyte-platelet (HALP) score on treatment response in hormone-positive metastatic breast cancer patients receiving cyclin-dependent kinase (CDK) 4/6 inhibitors.

Materials and Methods: This study was designed retrospectively. Between January 1, 2020, and September 30, 2023, 104 patients diagnosed with metastatic hormone receptor-positive/human epidermal growth factor 2 receptor negative breast cancer were treated with CDK4/6 inhibitors plus endocrine therapies at Sakarya University Training and Research Hospital. Patients were divided into two groups according to whether there was progression at the initial response evaluation. Factors that could predict treatment response between the two groups were compared with regression analysis.

Results: The median HALP score in patients was 34.08 (23.46-45.08) before treatment and 28.3 (19.24-42.61) at first response evaluation. Delta HALP was ≤0 for sixty-four (61.5%) patients, >0 for 40 patients (38.5%). There was no statistical difference in delta HALP score between groups with and without progression at the first response evaluation (p=0.334). The presence of liver metastasis and treatment line significantly affect the early progression by univariate and multivariate regression analysis (p=0.031 and p=0.016, respectively).

Conclusion: Our study has found that the delta HALP score does not predict early progression. The presence of liver metastasis and later treatment line were found to be statistically significant with early progression. These data are compatible with the literature.

Keywords: Cyclin-dependent kinase (CDK) 4/6 inhibitors, delta HALP score, hemoglobin-albumin-lymphocyte-platelet (HALP) score

ÖZ

Amaç: Bu çalışma, siklin bağımlı kinaz (CDK) 4/6 inhibitörleri alan hormon reseptörü pozitif/insan epidermal büyüme faktörü 2 reseptörü negatif (HR+/HER2-) metastatik meme kanseri hastalarında hemoglobin-albümin-lenfosit-trombosit (HALP) skorundaki tedavi başlangıcına göre olan değişimin tedavi yanıtını predikte edip etmediğini değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntem: Retrospektif olarak tasarlanan çalışmamıza Sakarya Üniversitesi Eğitim ve Araştırma Hastanesi'nde 1 Ocak 2020-30 Eylül 2023 tarihleri arasında HR+/HER2- metastatik meme kanseri tanısıyla CDK4/6 inhibitörü tedavisi alan 104 hasta dahil edildi. Hastalar ilk yanıt değerlendirmede progresyon durumuna göre iki gruba ayrıldı. İki grup arasında tedavi yanıtını predikte edebilecek klinik ve patolojik faktörler tek değişkenli ve çok değişkenli regresyon analizi ile karşılaştırıldı.

Bulgular: Hastaların ortalama HALP skoru CDK4/6 inhibitörü tedavisi öncesi 34,08 (23,46-45,08), ilk yanıt değerlendirmede 28,3 (19,24-42,61)

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idi. Altmış dört (%61,5) hastanın delta HALP değeri ≤0; 40 hastanın (%38,5) >0 olduğu görüldü. İlk yanıt değerlendirmede progresyon görülen ve görülmeyen hastalar arasında delta HALP skoru açısından istatistiksel fark saptanmadı (p=0,334). Karaciğer metastazı varlığı ve tedavi basamağının, tek değişkenli ve çok değişkenli regresyon analizinde erken progresyonu anlamlı olarak etkilediği görüldü (sırasıyla p=0,031; p=0,016).

Sonuç: Çalışmamıza göre delta HALP skoru erken progresyonu predikte etmemektedir. Karaciğer metastazı varlığı ve ileri basamaklarda kullanım erken progresyon için önemli iki risk faktörüdür. Bu veriler literatürle uyumludur.

Anahtar Kelimeler: Delta HALP skoru, hemoglobin-albümin-lenfosit-trombosit (HALP) skoru, siklin bağımlı kinaz (CDK) 4/6 inhibitörü

INTRODUCTION

Hormone receptor-positive/human epidermal growth factor 2 receptor negative (HR+/HER2-) patients account for 70% of all metastatic breast cancers. The metastasis is most commonly seen in the bone, lung, liver, and brain, respectively[1]. In HR+/HER2- metastatic breast cancer, a significant progression-free survival (PFS) benefit has been obtained with cyclin-dependent kinase 4/6 (CDK4/6) inhibitor and endocrine therapy combinations in the first-line treatment. The objective response rates (ORRs) with CDK4/6 inhibitors are 76%, yet a subset of patients fail to respond despite being classified as hormone positive[2,3].

Immunonutritional markers are valuable tools for predicting and assessing cancer progression and treatment response[4-6]. The hemoglobin-albumin-lymphocyte-platelet (HALP) score is a laboratory parameter that shows nutritional and inflammatory status. The HALP score is calculated as HALP score = [hemoglobin (g/L) × albumin (g/L) × lymphocytes (/L)]/ platelets (/L), which was first described in gastric cancer in 2015 and has been shown to be effective as a biomarker in many types of cancer[7,8].

The HALP score, a composite index reflecting nutritional and inflammatory status, has emerged as a potential prognostic biomarker in various cancer types, including metastatic hormone-positive breast cancer. A lower HALP score has been correlated with more aggressive disease progression and poorer outcomes in metastatic breast cancer patients[9,10].

This study aims to determine the predictive value of dynamic change in HALP score and also clinicopathological characteristics on treatment response in hormone-positive metastatic breast cancer patients receiving CDK4/6 inhibitors.

MATERIALS AND METHODS

Study Population

This retrospective study included 104 patients diagnosed with metastatic HR+, HER2- breast cancer who received CDK4/6 inhibitor plus ET at Sakarya University Training and Research Hospital between January 1, 2020 and September 30, 2023. Patients were aged 18 years or older, with confirmed ER and or PR positivity and HER2- metastatic breast cancer. Inclusion criteria required treatment with CDK4/6 inhibitors as first to fourth-line therapy. Patients were allowed to switch between CDK4/6 inhibitors due to allergy, tolerability, or drug availability. Male breast cancer patients and those without completed treatment response assessments were excluded. The study protocol was approved by the Ethics Committee of Sakarya University Medical Faculty (decision no: 27.06.2024-71522473-050.04-372954-165, date: 27.06.2024) and conducted according to the principles of the Declaration of Helsinki. Given the retrospective study design, the need for informed consent was waived.

This retrospective study analyzed patient data (demographic, clinicopathological, outcome, treatment response, and laboratory parameters) obtained from medical oncology outpatient clinic records, patient files, and electronic health records. Due to local insurance regulations, patients received either oral ribociclib or palbociclib in combination with fulvestrant, an aromatase inhibitor, or tamoxifen as endocrine therapy. Tumor response was evaluated locally every 12 weeks using RECIST 1.1 criteria from treatment initiation. Patients were categorized into two groups based on disease progression status at the initial response assessment.

Patients were evaluated for hemogram and biochemical blood parameters simultaneously. The HALP score was calculated, as [hemoglobin (g/L) × albumin (g/L) × lymphocytes (/L)]/ platelets (/L) at the beginning of CDK4/6 inhibitors and first response evaluation. PFS was defined as the time from the date of initiation of ribociclib or palbociclib until the date of radiological progression. Overall survival (OS) was defined as the time from the date of initiation of ribociclib or palbociclib to the date of death from any cause.

Statistical Analysis

All analyses were performed on SPSS version 23 (SPSS Inc., Chicago, IL, USA). Histogram and Q-Q plots were used to determine whether variables were normally distributed. Data are given as mean ± standard deviation or median (1st quartile - 3rd quartile) for continuous variables according to the normality of distribution and as frequency (percentage) for categorical variables. Between groups, an analysis of continuous variables was performed using the independent samples t-test or Mann-Whitney U test, depending on the normality of distribution. Age, gender, clinical

characteristics, laboratory results, and treatment methods were analyzed using univariate logistic regression. Then, the variables that were found significant were analyzed using the stepwise multivariate listening-reading method (enter method). The mean was employed to determine cut-off values for age. Survival times were calculated using the Kaplan-Meier method. Between groups, comparisons of survival times were performed using the log-rank test. ROC curve test was used to determine HALP's cut-off sign. P<0.05 values were accepted as statistically significant results.

RESULTS

A total of 104 patients were included in the study. The median age of the patients was 56±11.67 years (32-84). At the first response evaluation, 21 patients (%20) had progression. The median OS was 137.57 months [95% confidence interval (CI): 97.57-177.57]; the median PFS was 7.73 months (95% CI: 3.70-11.76) for all patients included in the study. All patients had a median HALP score of 34.08 (23.46-45.08) before treatment and 28.3 (19.24-42.61) at the first response evaluation Delta HALP was ≤0 for sixty-four (61.5%) patients and >0 for 40 patients (38.5%) was. There was no statistical difference in delta HALP score between groups with and without progression at the first response evaluation (p=0.334; Table 1). The cut-off value for the HALP score was 32.02 [area under the curve (AUC): 0.564]. At the beginning of treatment, 44 (42.3%) patients had a low HALP score, and 60 (57.7%) had a high score.

Patients who experienced early disease progression exhibited significantly higher mortality risk compared to those without progression (95% CI: 4.60-45.78, p<0.001). The median OS could not be calculated for patients without progression at the initial evaluation (95% CI: 100.15-256.56), while it was 13.43 months for patients with progression (95% CI: 12.65-99.21, p<0.001). A detailed comparison of patient characteristics between the two groups is presented in Table 1.

Survival Outcomes

The median OS was 110.87 months (95% CI: 56.62-166.12) for the palbociclib group and 137.57 months (95% CI: 100.81-174.33) for the ribociclib group. The median PFS was 8.2 months (95% CI: 3.14-13.26) for palbociclib and 7.6 months (95% CI: 5.30-9.9) for ribociclib. No statistically significant differences were observed in OS or PFS between the two treatment groups (p=0.888 and p=0.260, respectively) (Figure 1).

The presence of liver metastasis (LVM) and treatment line were statistically significant with early progression. The risk of early progression increased 4.03 times in patients with liver metastases (95% CI: 1.36-11.93; p=0.012). The progression risk was 6.24 times higher in patients receiving CDK4/6 inhibitors in the third and fourth lines (95% CI: 1.68-23.11; p=0.006).

Table 1. Comparison of clinical and pathological features of patients with and without progression at the first response evaluation

	Yes (n=21)	No (n=83)	p-value
	n (%)	n (%)	
Age (year)			
<56	12 (57.1)	40 (48.2)	0.464†
>56	9 (42.9)	43 (51.8)	
Menopause status			
Premenopause	10 (47.6)	32 (38.55)	0.572†
Postmenopause	11 (52.38)	51 (62.44)	
Delta HALP			
>0	10 (47.6)	30 (36.1)	0.334†
≤0	11 (52.4)	53 (63.9)	
Tumor location			
Left	9 (42.9)	47 (56.6)	0.528†
Right	11 (52.4)	33 (39.8)	
Left + Right	1 (4.8)	3 (3.6)	
Histology			
IDC	14 (66.7)	66 (79.5)	0.370†
ILC	5 (23.8)	10 (12.0)	
Others (IC. IDC+ILC. NOS)	2 (9.5)	7 (8.4)	
Progesterone receptor			
≥%1	21 (100.0)	75 (90.4)	0.139†
<%1	0 (0.0)	8 (9.6)	
HER2 status			
IHC score 1-2	5 (23.8)	25 (30.1)	0.568†
IHC score 0	16 (76.2)	58 (69.9)	
E-cadherin (IHC)			
Positive	11 (73.3)	29 (87.9)	0.210*
Negative	4 (26.7)	4 (12.1)	
Ki 67. labeling index. %			
<20	5 (35.7)	34 (54.0)	0.217†
≥20	9 (64.3)	29 (46.0)	
Nuclear grade			
1	3 (17.6)	20 (29.9)	0.241*
2	9 (52.9)	38 (56.7)	
3	5 (29.4)	9 (13.4)	
Neoadjuvant/ adjuvant treatment			
Yes	6 (28.6)	20 (24.1)	0.672†
No	15 (71.4)	63 (75.9)	
Operation primary tumor			
Yes	15 (72.4)	45 (54.2)	0.154†
No	6 (28.6)	38 (45.8)	
Bone metastasis			
Yes	15 (71.4)	70 (84.3)	0.17*
No	6 (28.6)	13 (15.7)	

Table 1. Continued

	Yes (n=21)	No (n=83)	
	n (%)	n (%)	p-value
Lung metastasis			
Yes	4 (19.0)	28 (33.7)	0.193†
No	17 (81.0)	55 (66.3)	
Liver metastasis			
Yes	8 (38.1)	11 (13.3)	**0.008***
No	13 (61.9)	72 (86.7)	
Brain metastasis			
Yes	1 (4.8)	3 (3.6)	0.807*
No	20 (95.2)	80 (96.4)	
Treatment line			
1-2	15 (71.5)	78 (94.0)	**0.003***
3-4	6 (28.5)	5 (6.0)	
CDK4/6 inhibitors			
Ribociclib	13 (61.9)	50 (60.2)	0.889*
Palbociclib	8 (38.1)	33 (39.8)	
Endocrine therapy			
Letrozole	9 (42.9)	50 (60.2)	0.34*
Fulvestrant	11 (52.4)	31 (37.3)	
Tamoxifene	1 (4.8)	2 (2.4)	
Dose reduction			
Yes	3 (14.3)	23 (27.7)	0.204†
No	18 (85.7)	60 (72.3)	
Exitus			
Yes	16 (76.2)	15 (18.1)	**<0.001†**
No	5 (23.8)	68 (81.9)	

HALP: Hemoglobin-albumin-lymphocyte-platelet, IDC: Invasive ductal carcinoma, ILC: Invasive lobular carcinoma, NOS: Not otherwise specified, HER2: Human epidermal growth factor receptor 2, IHC: Immunohistochemical, CDK: Cyclin dependent kinase. *Fisher's exact chi-square test, †Pearson chi-square test, bold mean p<0.05

The presence of LVM and treatment line also significantly affect the early progression by multivariate regression analysis (p=0.031; p=0.016; respectively) (Table 2).

DISCUSSION

CDK4/6 inhibitors (ribociclib, palbociclib, and abemaciclib) are first-line treatments in HR+/HER2- metastatic breast cancer. In our study, progression was observed in 20% of a total of 104 patients diagnosed with metastatic breast cancer using CDK4/6 inhibitors at the first response evaluation. Early progression was significantly higher in patients who had LVM and received CDK4-6 inhibitors treatment at the 3-4th line (p=0.012, p=0.006, respectively). However, there is no statistical difference in delta HALP score between groups with and without progression at the first response evaluation (p=0.334).

HALP score is a biomarker that indirectly shows immunological and nutritional status that may affect treatment response in metastatic breast cancer. In early-stage breast cancer, a low HALP score was associated with poor recurrence-free survival, axillary lymph node involvement at the surgical stage, and poor neoadjuvant treatment response. Pancytopenia due to CDK4/6 inhibitor and a history of chemotherapy may have affected the HALP score. However, the cut-off value is compatible with the literature and is 32.02 in our study[7,9-11].

The delta HALP score reflects the dynamic change in the patient's status and is thought to be more sensitive than the HALP score. Yuce et al.[12] evaluated whether delta HALP score predicted neoadjuvant treatment response in locally advanced breast cancer and obtained significant results like our study in all subgroups (HR+/-, HER2+/-).

Evaluating the first-line effectiveness of CDK4/6 inhibitors and paclitaxel treatment in patients with/impending visceral crisis in data, the ORR in the CDK4/6 inhibitors arm was 77.8% and it was observed that a rate like that in our study (22.2%) did not respond to treatment[13]. In addition, the fact that similar results were obtained in the 4-month disease control rate (77.8 % vs. 59.4%; p=0.168) and the time to first improvement (3.9 vs 3.6 weeks; p=0.773) between the two groups in this study suggests that chemotherapy cannot be an alternative to CDK4/6 inhibitors for preventing early progression. There is no clinicopathological or immunological biomarker to predict this aggressive group, and there is no statistical difference in delta HALP score between both groups (p=0.334).

The presence of liver metastases appears to be an essential risk factor for CDK4/6 inhibitor therapy. In a meta-analysis, the presence of liver metastases resistant to endocrine monotherapies was associated with poor outcomes, as in our study. This meta-analysis showed better outcomes for OS, PFS, and clinical benefit rate in the non-visceral metastasis group. The presence of LVM was associated with worse outcomes than patients with visceral non-liver metastases[14].

The fact that hormone receptor status was confirmed by biopsy before treatment in 90.4% of our patients and that HER2 receptor status was similar in both groups suggests that, apart from the available molecular data, changes in tumor biology, mainly caused by liver metastases, may be effective in early progression. We think an alternative/combined treatment to CDK4/6 inhibitors is required for this patient group.

Study Limitations

The most important limitations of our study are the heterogeneity of treatment lines and endocrine treatments, the inability to evaluate endocrine resistance mutations, the small number of patients, and the retrospective design.

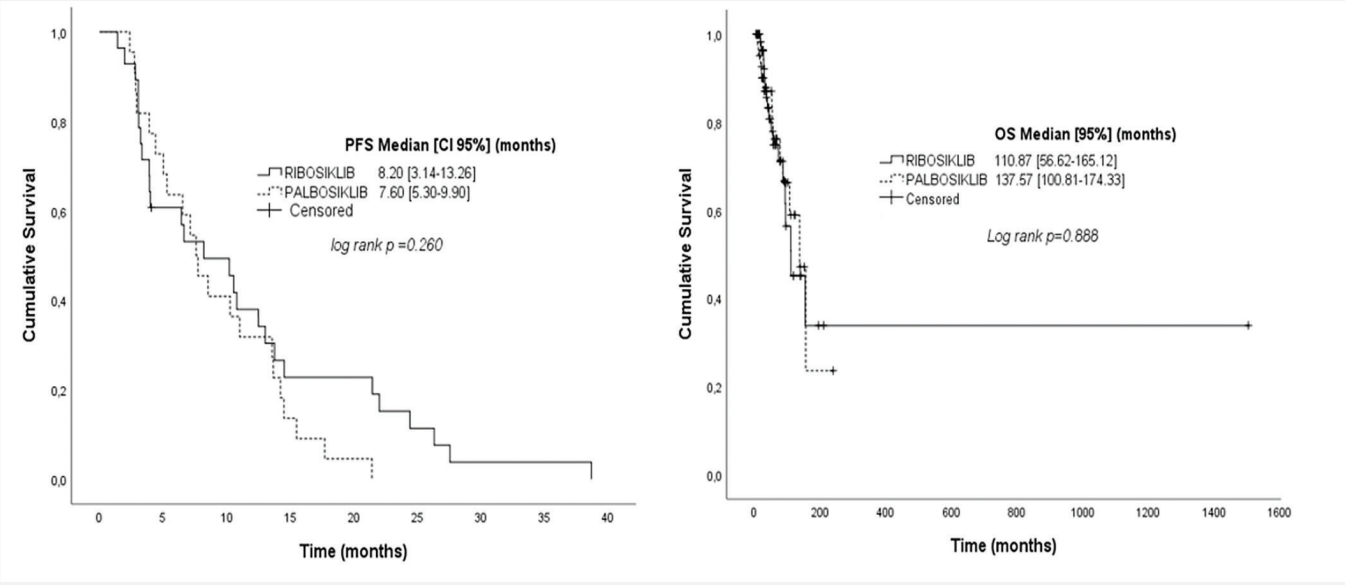

Figure 1. Comparison of PFS and OS Kaplan-Meier curves ribociclib and palbociclib

PFS: Progression-free survival, OS: Overall survival, CI: Confidence interval

Table 2. Univariate and multivariate regression analysis of clinical and pathological factors for early progression

	Univariate LR		Multivariate LR	
	OR (95% CI)	p	OR (95% CI)	p
Age >56 (ref ≤56)	0.69 (0.27-1.83)	0.465		
Delta HALP >0 (ref≤0)	1.61 (0.61-4.22)	0.337		
PR positive (ref: negative)	45.21 (0.01-155.15)	0.999		
HER2 score 1+ and 2+ (ref: score 0)	0.73 (0.24-2.19)	0.570		
Ki 67, % <20 (ref>20)	2.11 (0.64-7.01)	0.223		
Grade (ref: 1)		0.260		
2	1.58 (0.38-6.50)	0.527		
3	3.70 (0.72-18.97)	0.116		
Neoadjuvant/adjuvant chemotherapy history	1.26 (0.43-3.68)	0.673		
Operation with primary tumor	2.11 (0.75-5.98)	0.159		
Bone metastasis (ref: No)	0.46 (0.15-1.42)	0.178		
Lung metastasis (ref: No)	0.46 (0.14-1.51)	0.200		
Liver metastasis (ref: No)	4.03 (1.36-11.93)	**0.012**	3.50 (1.12-10.94)	**0.031**
Brain metastasis (ref: No)	1.33 (0.13-13.51)	0.808		
CDK treatment line 3-4 (ref: 1-2)	6.24 (1.68-23.11)	**0.006**	5.36 (1.37-20.89)	**0.016**
CDK type Ribociclib (ref: palbociclib)	0.93 (0.35-2.50)	0.889		
Dose reduction	0.44 (0.12-1.62)	0.214		

HALP: Hemoglobin-albumine-lymphocyte-platelet, PR: Progesterone receptor, HER2: Human epidermal growth factor receptor 2, ref: Reference; CDK: Cyclin dependent kinase, LR: Logistic regression, CI: Confidence interval, OR: Odds ratio

CONCLUSION

This retrospective study investigated the predictive value of the delta HALP score for early progression in metastatic breast cancer patients treated with CDK4/6 inhibitors. Our findings indicate that the delta HALP score is not a reliable predictor for early progression in this patient population. However, the presence of liver metastases and later treatment lines were significantly associated with an increased risk of early progression in patients receiving CDK4/6 inhibitors. These

results align with previous research highlighting the challenges in managing patients with metastatic breast cancer and the need for alternative therapeutic strategies.

Ethics

Ethics Committee Approval: The study protocol was approved by the Ethics Committee of Sakarya University Medical Faculty (decision no: 27.06.2024-71522473-050.04-372954-165, date: 27.06.2024) and conducted according to the principles of the Declaration of Helsinki.

Informed Consent: Given the retrospective study design, the need for informed consent was waived.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.B.G., Concept: B.B.G., M.Ö., E.Ö.E., F.A.K., E.Ç., İ.H., Design: B.B.G., M.Ö., E.Ö.E., F.A.K., E.Ç., İ.H., Data Collection or Processing: B.B.G., M.Ö., E.Ö.E., F.A.K., Analysis or Interpretation: B.B.G., E.Ç., İ.H., Literature Search: B.B.G., İ.H., Writing: B.G.

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REFERENCES

1. Wu Q, Li J, Zhu S, Wu J, Chen C, Liu Q, et al. Breast cancer subtypes predict the preferential site of distant metastases: a SEER based study. Oncotarget. 2017;8:27990-6.
2. Finn RS, Martin M, Rugo HS, Jones S, Im SA, Gelmon K, et al. Palbociclib and letrozole in advanced breast cancer. N Engl J Med. 2016;375:1925-36.
3. Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S, et al. Ribociclib as first-line therapy for hr-positive, advanced breast cancer. N Engl J Med. 2016;375:1738-48.
4. Ekinci F, Balcik OY, Oktay E, Erdogan AP. HALP score as a new prognostic index in metastatic renal cell cancer. J Coll Physicians Surg Pak. 2022;31:313-8.
5. Wang J, Jiang P, Huang Y, Tu Y, Zhou Q, Li N, et al. Prognostic value of the cut offs for halp in endometrial cancer. Am J Clin Oncol. 2023;46:107-13.
6. Zhang D, Chen S, Cao W, Geng N, Feng C. HALP score based on hemoglobin, albumin, lymphocyte and platelet can predict the prognosis of tongue squamous cell carcinoma patients. Heliyon. 2023;9:e20126.
7. Farag MC, Antar R, Akosman S, Ng M, Whalen MJ. What is hemoglobin, albumin, lymphocyte, platelet (HALP) score? A comprehensive literature review of HALP's prognostic ability in different cancer types. Oncotarget. 2023;14:153-72.
8. Chen XL, Xue L, Wang W, Chen HN, Zhang WH, Liu K, et al. Prognostic significance of the combination of preoperative hemoglobin, albumin, lymphocyte and platelet in patients with gastric carcinoma: a retrospective cohort study. Oncotarget. 2015;6:41370-82.
9. Duran A, Pulat H, Cay F, Topal U. Importance of HALP Score in breast cancer and its diagnostic value in predicting axillary lymph node status. J Coll Physicians Surg Pak. 2022;32:734-9.
10. Zhao Z, Xu L. Prognostic significance of HALP score and combination of peripheral blood multiple indicators in patients with early breast cancer. Front Oncol. 2023;13:1253895.
11. Lou C, Jin F, Zhao Q, Qi H. Correlation of serum NLR, PLR and HALP with efficacy of neoadjuvant chemotherapy and prognosis of triple-negative breast cancer. Am J Transl Res. 2022;14:3240-6.
12. Yuce E, Karakullukcu S, Bulbul H, Alandag C, Saygin I, Kavgaci H. The effect of the change in hemoglobin-albumin-lymphocyte-platelet scores occurring with neoadjuvant chemotherapy on clinical and pathological responses in breast cancer. Bratisl Lek Listy. 2023;124:59-63.
13. Behrouzi R, Armstrong AC, Howell SJ. CDK4/6 inhibitors versus weekly paclitaxel for treatment of ER+/HER2- advanced breast cancer with impending or established visceral crisis. Breast Cancer Res Treat. 2023;202:83-95.
14. Robertson JFR, Leo AD, Johnston S, Chia S, Bliss JM, Paridaens RJ, et al. Meta-analyses of visceral versus non-visceral metastatic hormone receptor-positive breast cancer treated by endocrine monotherapies. NPJ Breast Cancer. 2021;7:11.