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Factors affecting survival and recurrence in patients with operated non-small cell lung cancer

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Abstract

Aim: The most serious problem after curative treatment of non-metastatic lung cancer is disease recurrence. This study was designed to detect markers affecting disease recurrence and survival in operated lung cancer patients.

Materials and Methods: In this study, the data of 109 patients diagnosed with lung cancer were analyzed retrospectively. Cut-off values for neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), alkaline phosphatase (ALP), and gamma glutamyl transpeptidase (GGT) were determined by performing ROC Curve analysis. According to these cut-off values, the patients were divided into two groups. Based on the cut-off value of the markers, their effects on both overall survival (OS) and disease-free survival (DFS) were examined.

Results: In this study, the median OS of the patients was 53.9 months, and the median DFS was 20.6 months. The patients were re-evaluated by targeting the cut-off value of 2.35 for NLR obtained by ROC analysis. Below this value, mOS and mDFS were calculated as 78.2 and 43.2 months, respectively. Above this value, it was determined as 35.6 and 20.6 months, respectively. A similar evaluation was made for the PLR. As a result of the ROC analysis, the cut-off value was determined as 124.7. Below this value, mOS and mDFS were calculated as 72.4 and 36.9 months, respectively. Above this value, it was determined as 41.7 and 21.8 months, respectively. Both results were statistically significant ($p<0.05$).

Conclusion: This study showed that NLR and PLR predict statistical significance for OS and DFS.

Introduction

Lung cancer is one of the most frequently detected malignancies worldwide and is the leading cause of cancer-related death [1]. Despite recent advances in treatment options, including molecularly targeted agents and immune checkpoint inhibitors, the average 5-year relative survival rate for lung cancer patients is only about 17% [2]. These poor survival rates may be due to two main reasons. These reasons are that the patients were diagnosed at a more advanced stage and that the patients relapsed after definitive treatment. The follow-up of patients after definitive treatment is carried out with the current recommendations of international guidelines. However, it may not be possible to detect recurrences in the early period due to the inadequacy of conventional imaging methods. For this purpose, the concept of biochemical recurrence, which is detected before radiological recurrence, gains importance. There is a definition of minimal residual disease (MRD), which cannot be reliably detected by conventional radiological imaging studies due to poor resolution, but is an important source for early recurrence and metastasis [3].

As known from previous studies, inflammatory prognostic markers (IPM) have an important place in both the prognosis and prediction of the disease. The most well-known of these inflammatory prognostic markers are neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) and Pan-Immune-Inflammation score. Immune cells in the tumor microenvironment are associated with improved outcome. The most important of these cells are cytotoxic CD8 T cells. Among the immune cells associated with tumor progression and poor prognosis, the best known are neutrophils, M2 polarized macrophages, and FOXP3 positive regulatory T cells [4-6]. In addition to all these cell elements, platelets are also part of an inflammatory process and thus thrombocytosis is common in solid tumors [7].

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These inflammatory prognostic markers, obtained by the ratios of the measurements of these cell elements in the peripheral blood, have been shown to be associated with survival in most cancer types, including lung cancer [8]. The mechanism of the relationship between the systemic inflammatory response and the progression of cancer is clearly known. One reason for this correlation is that tumor growth in patients with high NLR may be promoted by neutrophil-derived cytokines such as vascular endothelial growth factor, interleukin-18, and matrix metalloproteinases. In addition, increased neutrophils around the tumor may be due to natural killer cells and activated T cells suppressing anti-tumor immune responses. Concomitantly, lymphocyte-mediated anti-tumor cellular immune response may be weakened due to decreased lymphocytes around the tumor. Therefore, the coexistence of neutrophilia and lymphocytopenia causes a high NLR. Thus, it is likely to promote angiogenesis and inhibit antitumor reactivity, ultimately promoting tumor growth and progression [9-11].

Our aim in this study is to investigate the effectiveness of inflammatory prognostic markers such as NLR and PLR on parameters such as disease-free survival and overall survival in patients with operated lung cancer.

Materials and Methods

Study population

In this study, the data of 109 lung cancer patients who were operated on in our hospital between 2013 and 2020 were analyzed retrospectively. Patients over the age of 18 were included in our study. Patients who received neoadjuvant therapy before surgical treatment were excluded from the study as it may alter the pathological staging. In addition, patients with missing laboratory parameters required for our study before surgery and patients with a previous cancer diagnosis were excluded from the study. Patients had no preoperative hematological disease or infection. Patients were classified according to age, gender, type of imaging, pathological subtype, and type of operation, pathological staging, differentiation, and adjuvant chemotherapy status. In addition, some inflammatory prognostic markers obtained using the laboratory parameters of the patients were also evaluated in the study. The first of these parameters, NLR = absolute neutrophil count / absolute lymphocyte count was calculated. Another inflammatory prognostic marker, PLR= absolute platelet count/absolute lymphocyte count was calculated. DFS was calculated in months based on the time to relapse in patients who completed their postoperative systemic therapy in relapsed patients. OS was evaluated by calculating the time from diagnosis to death in months during the follow-up period. All procedures performed in studies involving human participants were under the national research committee's ethical standards and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Before the study, ethical approval was obtained from the Inonu University Clinical Research Ethics Committee (Decision number: 2022/2881, Date: 11.01.2022).

Statistical analysis

IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp. program was used for the statistical analysis of the data. Categorical measurements were summarized as numbers and percentages, and continuous measurements as median and standard deviation (median and minimum-maximum where appropriate). Shapiro-Wilk test was used to determine whether the parameters in the study showed a normal distribution. Kaplan-Meier method and Log Rank tests were used for survival analysis. The sensitivity and specificity values for Alkaline phosphatase (ALP), Gamma Glutamyl Transpeptidase (GGT), NLR, and PLR values were calculated based on the mortality variable of the patients included in the study, and the cut-off value was determined by examining the area under the ROC curve. The statistical significance level was taken as 0.05 in all tests.

Results

Considering the inclusion and exclusion criteria, the data of 109 patients were retrospectively analyzed and included in the study. The clinicopathological features of the patients are shown in Table 1. The relationship between radiological examination, pathological subtype and disease stage of the patients and survival (months) is shown in

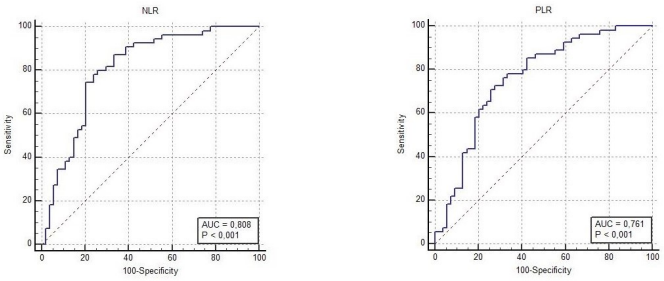

Figure 1. NLR and PLR ROC Curve.

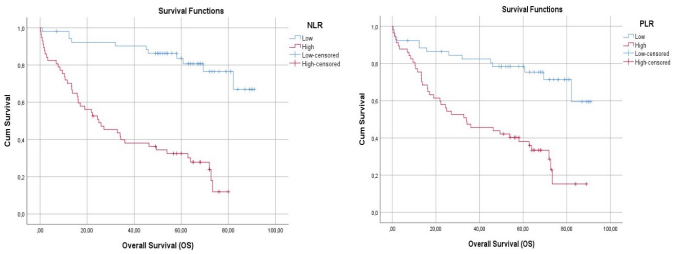

Figure 2. NLR and PLR OS.

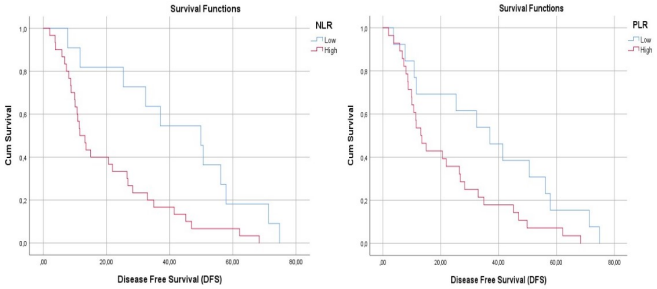

Figure 3. NLR and PLR DFS.

Table 1. The Clinico-pathological features of the patients.

	N (number of patients)	%
Sex		
Male	95	87.2
Female	14	12.8
Radiological Examination		
CT	48	44.0
PET/CT	61	56.0
Tumor subtype		
Squamous Cell Carcinoma	56	51.3
Adenocarcinoma	51	46.8
Large Cell Carcinoma	2	1.9
Tumor Location		
Right Lung Upper Lobe	27	24.8
Right Lung Mid Lobe	8	7.3
Right Lung Lower Lobe	28	25.7
Left Lung Upper Lobe	28	25.7
Left Lung Lower Lobe	18	16.5
Lymph Node Status		
Positive	51	46.8
Negative	58	53.2
Recurrence		
Yes	41	37.6
No	68	62.4
Stage		
Stage I	36	33
Stage II	39	35.7
Stage III	34	31.3
Type of operation		
Lobectomy	62	56.9
Wedge Resection	12	11.0
Pneumonectomy	24	22.0
Other	11	10.1
Lymph vascular Invasion Positive	63	57.8
Perineural Invasion Positive	35	32.1
Differentiation		
Good Differentiation	28	25.7
Middle Differentiation	37	33.9
Poorly Differentiation	42	38.5
Other	2	1.8
Adjuvant Chemotherapy		
Yes	53	48.6
No	35	32.2
Could not receive	9	8.2
Postoperative Exitus	6	5.5
Data Not Available	6	5.5
Current status of the patient		
Alive	55	50.5
Exitus	54	49.5

Table 2. The Relationship between Radiological Examination, Pathological Subtype, and Disease Stage with Survival (Month).

	Mean ±std	%95 CI		p
		Lower Limit	Upper Limit	
Radiological Selection (OS)				
CT	56.1 ±5.2	46.0	66.2	0.821
PET/CT	57.3 ±4.7	48.2	66.5	
Radiological Selection (DFS)				
CT	33.7 ±4.8	24.2	43.1	0.012*
PET/CT	18.5 ±3.8	11.1	25.9	
Tumor Type (OS)				
Squamous	57.1 ±5.0	47.2	67.0	
Adenocarcinoma	57.4 ±4.9	47.8	67.0	0.490
Other+	39.1 ±13.1	13.4	64.8	
Tumor Type (DFS)				
Squamous	24.9 ±4.5	16.2	33.8	
Adenocarcinoma	28.9 ±5.0	19.0	38.8	0.340
Other+	9.9 ±1.0	9.9	9.9	
Stage (OS)				
Stage I	69.3 ±5.3	58.9	79.7	
Stage II	52.1 ±5.8	40.7	63.5	0.046*
Stage III	47.5 ±6.3	35.3	59.8	
Stage (DFS)				
Stage I	33.2 ±7.2	19.1	47.3	
Stage II	24.9 ±5.9	13.3	36.6	0.600
Stage III	24.1 ±4.5	15.2	32.9	

Table 2. The relationship between NLR and PLR, which is one of the main research subjects of our study, and survival was also evaluated. ROC analysis and ROC curve were created to establish a cut-off value for NLR and PLR values. The patients were divided into two groups according to survival and ROC analysis was performed according to these groups. As a result of the ROC analysis, the area under the ROC curve was calculated as 80.8%. According to this cut-off value we determined, it is assumed that if the NLR value is 2.35 and below, it has a positive effect on overall survival with 74.6% sensitivity and 79.6% specificity. According to the determined cut-off value, it is assumed that if the PLR value is 124.7 and below, it affects the survival with 70.9% sensitivity and 74.1% specificity. In addition, the Kaplan Meier plot showing ROC curve analysis of NLR and PLR is shown in Figures 1. As a result, both NLR and PLR are statistically significantly predictive for survival parameters using threshold values obtained using ROC curve analysis. The relationship of NLR and PLR with OS is shown in Figure 2 with Kaplan Meier curves. The relationship of NLR and PLR with DFS is shown in Figure 3 with Kaplan Meier curves. It is known that elevated ALP and GGT levels are badly associated

Table 3. Association of NLR, PLR, ALP, and GGT with Survival (Month).

	Mean ±std	p
NLR (OS)		
<2.35	78.2±3.6	<0.001*
>2.35	35.6±3.9	
NLR (DFS)		
<2.35	43.2±6.7	0.006*
>2.35	20.6±3.2	
PLR (OS)		
<124.7	72.4±4.4	<0.001*
>124.7	41.7±4.3	
PLR (DFS)		
<124.7	36.9±6.7	0.035*
>124.7	21.8±3.4	
ALP (OS)		
<112	61.9±3.9	0.001*
>112	38.3±6.4	
ALP (DFS)		
<112	29.6±4.2	0.101
>112	20.3±5.1	
GGT (OS)		
<25	48.8±4.9	0.080
>25	60.8±4.5	
GGT (DFS)		
<25	26.4±4.7	0.912
>25	26.8±4.8	

with survival in metastatic diseases. In this study, we also aimed to evaluate whether it is associated with survival in early-stage disease. The relationship between ALP and GGT, another research topic of our study, with survival times was also evaluated. To establish a cut-off value for ALP and GGT values, ROC analysis and ROC curve were created and divided into two groups according to survival. A statistically significant relationship between ALP and DFS and GGT with both OS and DFS could not be determined. The cut-off values for NLR, PLR, ALP and GGT and all survival information for these values are shown in Table 3.

Discussion

The curative treatment of patients with early-stage lung cancer is a complete surgical resection with mediastinal lymph node dissection [12]. Our aim in this study is to find out whether there is a statistically significant difference in terms of DFS and OS based on IPMs in operated lung cancer patients. For this purpose, the parameters used in our study can guide patient selection. In particular, inflammatory prognostic markers are known to be directly related to survival in most cancer types. Comprehensive meta-analyses regarding this have been reported in the literature [13,14]. Similarly, a recent study showed that patients with Stage-I lung cancer with low PLR had a better survival [15]. In previous studies on gastric cancer, the NLR value was calculated using the parameters obtained from the peripheral blood count of the patients in the pre-operative period. These studies have shown that OS is worse in patients with high pre-operative NLR. The pathogenesis responsible for this condition is that systemic inflammatory responses with an elevated NLR increase the generation of inflammatory cytokine cascades, including tumor necrosis factor- α and interleukin-1, interleukin-6, and interleukin-8-related cascades. These immune modulators can affect the function and regulation of natural killer cells, cytotoxic T lymphocytes and antigen presenting cells. As a result, micrometastases can progress rapidly during periods of short- or long-term relative immunosuppression resulting from postoperative complications [16,17].

Inflammatory prognostic markers such as NLR are not only indicators for improved surveillance in operated patients. Although neoadjuvant therapy is not a standard method for operable lung cancer, a study conducted in 2016 also showed that NLR is associated with the response of neoadjuvant therapy. In this study, the rate of pathological response after neoadjuvant therapy in patients with low NLR was found to be statistically significantly higher than in patients with high NLR [18]. In addition, studies showing that NLR is associated with surveillance are not limited to chemotherapy. A new analysis was performed on the data of patients receiving durvalumab after definitive chemoradiotherapy in stage III lung cancer patients. As a result of this analysis, it was determined that patients with low NLR had a better PFS [19]. Similar results are also valid for PLR. In a study conducted in 2018, patients were divided into two groups by calculating preoperative PLR values. In this study, patients with low PLR's were found to have statistically significantly better 5- and 10-year survival outcomes compared to the group with high PLR's [20]. In another recently published study, patients with stage IA-IIIA who underwent surgery and in post-operative pathology were included in the study. In this study, patients were classified according to their PLR and NLR values. Both prognostic markers were found to be directly related to survival [21]. It is clearly seen that NLR and PLR, which were evaluated in our study, are two important inflammatory prognostic markers. In this study, ROC curve analysis was used to determine cut-off values. It was determined as 2.35 and 127.4, respectively. Both OS and DFS data of the patients found below these values were found to be statistically significant. By evaluating these parameters in patients who have completed surgical treatment for lung cancer, closer follow-up can be planned for high-risk patients in terms of recurrence. In addition to the radiological follow-up of these patients, molecular recurrence can be followed by ctDNA measurements. In the literature review, it was determined that there was a study related to this situation. In this study, NLR, PLR, and ctDNA were evaluated with both OS and PFS in metastatic pancreatic cancer patients. All three markers were found to have a direct statistically significant relationship with both OS and PFS. NLR was also found to correlate with ctDNA [22]. However, not all data

in the literature support that these IPMs are positively associated with survival. In a study on pancreatic cancer, no significant relationship was found between IPMs and survival [23]. However, when we look at these studies in general, there are retrospective studies with large patient numbers showing the relationship of these IPMs with survival. To use the available opportunities most effectively, a risk score should be made and a different treatment and post-treatment follow-up plan should be prepared for each patient. A similar scoring system has been used for Renal Cell Cancer (RCC) for a long time. Patients are treated according to the data obtained from this scoring system. In metastatic RCC, the survival of patients can be predicted by using the IMDC score [24]. According to this scoring system, patients are classified as favorable, intermediate, and poor prognostic, and their treatment is determined according to this plan. We support the idea that we can use a similar situation in other cancer patients. It is possible to optimally plan the adjuvant treatment given as a result of the calculation of the clinical risks of the patients. In addition, these patients can be grouped by clinical risk calculation and their follow-up can be done in accordance with these risk groups.

We performed a similar evaluation based on the ALP and GGT values of the patients. In the ROC curve analysis, the cut-off values for ALP and GGT were determined as 112 and 25, respectively. While no statistically significant result could be reached for both OS and DFS for GGT, it was determined that there was a statistically significant survival contribution for OS in patients below the cut-off value for ALP. A numerical improvement was found for DFS without any statistical significance. Studies in the literature have shown that ALP is associated with lower survival, especially in prostate cancer patients with bone metastases [25,26]. In this study, all patients were patients with early-stage lung cancer who had undergone surgery and had no metastases. Despite this situation, when the ALP elevation in these patients were evaluated based on the cut-off value, it was seen that it contributed to survival, which was statistically significant for OS.

There are also some limitations of this study. These limitations are the low number of patients, retrospective trial, the inclusion of patient data from a single center, and the lack of standardization of surgical procedures applied to patients.

Conclusion

Consequently, until the cost of ctDNA measurement is reasonable to evaluate in each patient, a specific scoring system should be used for both adjuvant therapy and post-treatment relapse follow-up. In this scoring system, inflammatory prognostic markers such as NLR and PLR can be used, as well as easily accessible laboratory parameters such as ALP. We think that this study that we have completed will contribute to the literature in terms of giving ideas for future studies.

Ethics approval

Ethical approval was obtained from the Inonu University Clinical Research Ethics Committee (Decision number: 2022/2881, Date: 11.01.2022).

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians. 2018;68(6):394-424.
2. Zhao Y, Varn FS, Cai G, Xiao F, Amos CI, Cheng C. A P53-Deficiency gene signature predicts recurrence risk of patients with early-stage lung adenocarcinoma. Cancer Epidemiology Biomarkers and Prevention. 2018;27(1):86-95.
3. Qiu B, Guo W, Zhang F, Lv F, Ji Y, Peng Y et al. Dynamic recurrence risk and adjuvant chemotherapy benefit prediction by ctDNA in resected NSCLC. Nature Communications. 2021;12(1).
4. C.I. Diakos, K.A. Charles, D.C. McMillan, S.J. Clarke, Cancer-related inflammation and treatment effectiveness, Lancet Oncol. 15 (2014) e493–e503, http://dx.doi. org/10.1016/S1470-2045(14)70263-3.
5. A. Yuan, Y.-J. Hsiao, H.-Y. Chen, H.-W. Chen, C.-C. Ho, Y.-Y. Chen, et al., Opposite effects of M1 and M2 macrophage subtypes on lung cancer progression, Sci. Rep. 5 (2015) 14273.
6. H. Tao, Y. Mimura, K. Aoe, S. Kobayashi, H. Yamamoto, E. Matsuda, et al., Prognostic potential of FOXP3 expression in non-small cell lung cancer cells combined with tumor-infiltrating regulatory T cells, Lung Cancer 75 (2012) 95–101.
7. R.L. Stone, A.M. Nick, I.A. McNeish, F. Balkwill, H.D. Han, J. Bottsford-Miller, et al., Paraneoplastic thrombocytosis in ovarian cancer, N. Engl. J. Med. 366 (2012) 610–618.
8. Diem S, Schmid S, Krapf M, Flatz L, Born D, Jochum W et al. Neutrophil-to-Lymphocyte ratio (NLR) and Platelet-to-Lymphocyte ratio (PLR) as prognostic markers in patients with non-small cell lung cancer (NSCLC) treated with nivolumab. Lung Cancer. 2017 Sep;111:176-181.
9. Yamanaka T, Matsumoto S, Teramukai S, Ishiwata R, Nagai Y, Fukushima M. The baseline ratio of neutrophils to lymphocytes is associated with patient prognosis in advanced gastric cancer. Oncology 2007;73:215e20.
10. Shimada H, Takiguchi N, Kainuma O, Soda H, Ikeda A, Cho A, et al. High preoperative neutrophil-lymphocyte ratio predicts poor survival in patients with gastric cancer. Gastric Cancer 2010;13:170e6.
11. Jung MR, Park YK, Jeong O, Seon JW, Ryu SY, Kim DY, et al. Elevated preoperative neutrophil to lymphocyte ratio predicts poor survival following resection in late stage gastric cancer. J Surg Oncol 2011;104:504e10.
12. Chansky K, Detterbeck FC, Nicholson AG, Rusch VW, Vallières E, Groome P et al. The IASLC Lung Cancer Staging Project: External Validation of the Revision of the TNM Stage Groupings in the Eighth Edition of the TNM Classification of Lung Cancer. Journal of Thoracic Oncology. 2017;12(7):1109-1121.
13. Zhou Q, Su S, You W, Wang T, Ren T, Zhu L. Systemic Inflammation Response Index as a Prognostic Marker in Cancer Patients: A Systematic Review and Meta-Analysis of 38 Cohorts. Dose-Response. 2021;19(4).
14. Winther-Larsen A, Aggerholm-Pedersen N, Sandfeld-Paulsen B. Inflammation-scores as prognostic markers of overall survival in lung cancer: a register-based study of 6,210 Danish lung cancer patients. BMC Cancer. 2022;22(1).
15. Mizuguchi S, Izumi N, Tsukioka T, Komatsu H, Nishiyama N. Neutrophil-lymphocyte ratio predicts recurrence in patients with resected stage 1 non-small cell lung cancer. J Cardiothorac Surg. 2018 27;13(1):78.
16. Li QG, Li P, Tang D, Chen J, Wang DR. Impact of postoperative complications on long-term survival after radical resection for gastric cancer. World J Gastroenterol 2013;19:4060e5.
17. Kubota T, Hiki N, Nunobe S, Kumagai K, Aikou S, Watanabe R, et al. Significance of the inflammation-based Glasgow prognostic score for short- and long-term outcomes after curative resection of gastric cancer. J Gastrointest Surg 2012;16:2037e44.
18. Chen Y, Chen K, Xiao X, Nie Y, Qu S, Gong C et al. Pretreatment neutrophil-to-lymphocyte ratio is correlated with response to neoadjuvant chemotherapy as an independent prognostic indicator in breast cancer patients: a retrospective study. BMC Cancer. 2016 19;16:320.
19. Bryant AK, Sankar K, Strohbehn GW, Zhao L, Elliott D, Qin A el al. Prognostic and predictive value of neutrophil-to-lymphocyte ratio with adjuvant immunotherapy in stage III non-small-cell lung cancer. Lung Cancer. 2022 ;163:35-41.

20. Toda M, Tsukioka T, Izumi N, Komatsu H, Okada S, Hara K et al. Platelet-to-lymphocyte ratio predicts the prognosis of patients with non-small cell lung cancer treated with surgery and postoperative adjuvant chemotherapy. Thorac Cancer. 2018;9(1):112-119.
21. Łochowski M, Chałubińska-Fendler J, Zawadzka I, Łochowska B, Rębowski M, Brzeziński D et al. The Prognostic Significance of Preoperative Platelet-to-Lymphocyte and Neutrophil-to-Lymphocyte Ratios in Patients Operated for Non-Small Cell Lung Cancer. Cancer Manag Res. 2021 9;13:7795-7802.
22. Toledano-Fonseca M, Teresa Cano M, Inga E, Gómez-España A, Guil-Luna S, García-Ortiz MV et al. The combination of neutrophil–lymphocyte ratio and platelet–lymphocyte ratio with liquid biopsy biomarkers improves prognosis prediction in metastatic pancreatic cancer. Cancers (Basel). 2021;13(6):1-17.
23. Chawla A, Huang TL, Ibrahim AM, Hardacre JM, Siegel C, et al. Pretherapy neutrophil to lymphocyte ratio and platelet to lymphocyte ratio do not predict survival in resectable pancreatic cancer. HPB (Oxford). 2018 May;20(5):398-404.
24. Jiang G, Chen S, Chen M. Exploration of IMDC model in patients with metastatic renal cell carcinoma using targeted agents: a meta-analysis. Int Braz J Urol. 2020 May-Jun;46(3):328-340.
25. Heinrich D, Bruland O, Guise TA, Suzuki H, Sartor O. Alkaline phosphatase in metastatic castration-resistant prostate cancer: Reassessment of an older biomarker. Future Oncology. 2018;14(24):2543-2556.
26. van der Doelen MJ, Stockhaus A, Ma Y, Mehra N, Yachnin J, Gerritsen WR et al. Early alkaline phosphatase dynamics as biomarker of survival in metastatic castration-resistant prostate cancer patients treated with radium-223. Eur J Nucl Med Mol Imaging. 2021 Sep;48(10):3325-3334.