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ABSTRACT

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INFLAMMATORY MARKERS AS PREDICTORS OF EFFICACY OF BEVACIZUMAB AND TYROSINE KINASE INHIBITORS THERAPY IN METASTATIC NON-SMALL CELL LUNG CANCER PATIENTS

Introduction. An essential role in the formation and development of non-small cell lung cancer (NSCLC) is played by systemic inflammation, which indirectly affects neoangiogenesis, proliferation, disease recurrence, and tumor spreading and can modulate the response to medication therapy. Clinical monitoring of inflammatory markers may help predict the outcome of the disease and allow select the most suitable candidates for targeted therapy of metastatic NSCLC (mNSCLC).

The study aimed to establish independent predictors of the efficacy of bevacizumab and tyrosine kinase inhibitors (TKIs) therapy affecting progression-free survival (PFS) and overall survival (OS) in mNSCLC patients.

Materials and methods. One hundred nine patients with mNSCLC who received bevacizumab or TKI therapy at the Sumy Regional Clinical Oncology Center participated in the retrospective study. We obtained data on patients' age, gender, body mass index, smoking status, number of metastases and their localization, category T and category N, and the applied treatment regimen from primary medical records. Based on complete blood count and chemistry tests, inflammatory indices were calculated: neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), metastatic lung cancer index (ALI), prognostic nutritional index (PNI), systemic inflammation index (SII) and index of hemoglobin, albumin, lymphocytes, and platelets (HALP). ROC analysis was used to establish the predictive value of indices and cut-off values. The Kaplan-Meier method and the Log-rank test assessed the effect on survival. Multivariate Cox regression analysis was used to determine independent predictors of treatment efficacy.

The results. SII demonstrated a statistically significant impact on PFS and OS. Patients with low SII had longer PFS (Log-rank 0.0016) and OS (Log-rank P=0.0083). Median PFS in patients with low SII was 9.8 months versus 7.0 months in patients with high SII. Median OS in patients with low SII was 13.9 months versus 9.1 months in patients with high SII. Smoking status (P=0.001), category N (P=0.034), and SII (P=0.018) can be considered independent predictors of PFS and OS. Patients with high SII, current and former smokers, and those whose category N is 2 or 3 have a worse prognosis.

Conclusions. SII is an independent predictor of the efficacy of bevacizumab and TKI therapy affecting PFS and OS in mNSCLC patients. A low SII correlates with better survival and a favorable impact on patient outcomes. In addition to SII, smoking status and category N are independent predictors of survival.

Keywords: non-small cell lung cancer, markers of inflammation, survival, bevacizumab, systemic inflammation index.

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РЕЗЮМЕ

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МАРКЕРИ ЗАПАЛЕННЯ ЯК ПРЕДИКТОРИ ЕФЕКТИВНОСТІ ТЕРАПІЇ БЕВАЦИЗУМАБОМ ТА ІНГІБІТОРАМИ ТИРОЗИНКІНАЗИ У ПАЦІЄНТІВ З МЕТАСТАТИЧНИМ НЕДРІБНОКЛІТИННИМ РАКОМ ЛЕГЕНЬ

Резюме. Важливу роль у формуванні та розвитку недрібноклітинного раку легень (НДКРЛ) відіграє системне запалення, яке опосередковано впливає на неоангіогенез, проліферацію, рецидивування та поширення пухлини та моделює відповідь на медикаментозну терапію. Клінічний моніторинг маркерів запалення може бути корисним для прогнозування перебігу захворювання та відбору найбільш відповідних кандидатів для таргетної терапії метастатичного НДКРЛ (мНДКРЛ).

Метою дослідження було встановити незалежні предиктори ефективності терапії бевацизумабом та інгібіторами тирозинкінази (ІТК), що впливають на виживаність без прогресування (ВБП) та загальну виживаність (ЗВ) у пацієнтів з мНДКРЛ.

Матеріали та методи. У ретроспективному дослідженні прийняли участь 109 пацієнтів із мНДКРЛ, що отримували терапію бевацизумабом або ІТК в Сумському обласному клінічному онкологічному центрі. Дані про вік, стать пацієнтів, індекс маси тіла, статус паління, кількість метастазів та їх локалізацію, категорію Т та категорію N, застосовувану лікувальну схему отримували з первинної медичної документації. На підставі повного клінічного та біохімічного аналізів крові розраховували індекси запалення: нейтрофільно-лімфоцитарне співвідношення (NLR), тромбоцитарно-лімфоцитарне співвідношення (PLR), індекс метастатичного раку легень (ALI), прогностичний харчовий індекс (PNI), індекс системного запалення (SII) та індекс гемоглобіну, альбуміну, лімфоцитів та тромбоцитів (HALP). Для встановлення прогностичної цінності індексів та граничних значень використовували ROC-аналіз. Вплив на виживаність оцінювали методом Каплана-Майєра та Log-rank тестом. Для визначенні незалежних предикторів ефективності терапії використовували багатофакторний регресійний аналіз Кокса.

Результати. Серед досліджуваних маркерів запалення статистично достовірний вплив на ВБП та ЗВ продемонстрував SII. Пацієнти з низьким SII мали кращу ВБП (Log-rank 0,0016) та ЗВ (Log-rank P=0,0083). Медіана ВБП у пацієнтів з низьким SII була 9,8 місяців проти 7 місяців у пацієнтів з високим SII. Медіана ЗВ у пацієнтів з низьким SII була 13,9 місяців проти 9,1 місяців у пацієнтів з високим SII. Незалежними предикторами ВБП та ЗВ можна вважати статус паління (P=0,001), категорію N (P=0,034) та SII (P=0,018). Пацієнти з високим SII, теперішні та колишні курці та ті, чия категорія N становить 2 або 3 мають гірший прогноз.

Висновки. SII є незалежним предиктором ефективності терапії бевацизумабом та ІТК, що впливає на ВБП та ЗВ у пацієнтів з мНДКРЛ. Низький SII корелює із кращою виживаністю та сприятливим перебігом захворювання. Крім SII, прогностичними факторами є статус паління та категорія N.

Ключові слова: недрібноклітинний рак легень, маркери запалення, виживаність, бевацизумаб, індекс системного запалення.

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INTRODUCTION

Lung cancer is one of the unsolved problems in medicine. Despite the rapid development of clinical oncology, treatment results remain disappointing, especially for patients in the advanced stages. According to the data of the National Cancer Registry of Ukraine, about 46% of patients at the time of diagnosis have stage IV [1]. An essential role in the formation and development of non-small cell lung cancer (NSCLC) is played by systemic inflammation, which indirectly affects neoangiogenesis, proliferation, disease recurrence, and tumor spreading and can modulate the response to medication therapy [2, 3, 4].

The most common laboratory markers of systemic inflammation are lymphocytes, monocytes, neutrophils, C-reactive protein, and indices based on these parameters, such as the ratio of neutrophils to lymphocytes (NLR), monocytes to lymphocytes (MLR), and platelets to lymphocytes (PLR).

The outcomes of NSCLC can depend on nutritional status, reflected in laboratory parameters such as serum albumin level. Albumin has anti-inflammatory activity and can reduce the level of systemic inflammation to some extent [6]. Hypoalbuminemia is associated with low survival and poor prognosis in mNSCLC patients [7]. To more correctly reflect the state of nutrition and the level of systemic inflammation, indices based on the serum albumin level are used, which allow the combined effect of various laboratory parameters to be considered. In particular, the prognostic nutrition index (PNI) [8], the inflammatory index of advanced lung cancer (ALI) [9], and the hemoglobin, albumin, lymphocyte, and platelet (HALP) scale [10] are recognized as predictors of the effectiveness of immune checkpoint inhibitor therapy and radical surgical treatment in NSCLC patients. Clinical monitoring of inflammatory markers may help predict the outcome of the disease and allow select the most suitable candidates for targeted therapy of metastatic NSCLC (mNSCLC).

The current study aimed to establish independent predictors of the efficacy of bevacizumab and tyrosine kinase inhibitors (TKIs) therapy affecting progression-free survival (PFS) and overall survival (OS) in mNSCLC patients.

MATERIALS AND METHODS

Research design. One hundred nine patients with mNSCLC who received bevacizumab or TKI therapy at the Sumy Regional Clinical Oncology Center were enrolled in a retrospective study. Inclusion criteria were age older than 18 years, histologically confirmed NSCLC, metastatic stage of NSCLC, bevacizumab-based or TKI-based treatment regimen (minimum two cycles), and available results of complete blood count tests and chemistry tests before starting bevacizumab or TKI therapy. The exclusion criteria were the treatment regimen without bevacizumab or TKI, small cell lung cancer, early NSCLC, infectious, autoimmune, or inflammatory diseases within two weeks before the start of systemic anticancer therapy, the development of other malignancies, incomplete results of blood count tests and chemistry tests. The study was approved by the Local Ethics Committee of the Sumy Regional Clinical Oncology Center (protocol 2/3, dated January 15, 2024). It was conducted following the ethical principles of the Declaration of Helsinki.

Assessment of response to treatment and follow-up period. To assess the response to treatment, all patients underwent computed tomography every 2–3 cycles according to local practice. Research results were analyzed according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1). A complete response to treatment (CR) was considered complete disappearance of the primary tumor and metastases, stabilization of the disease (SD) – a decrease in tumor burden by less than 30% or an increase by less than 20%, partial response (PR) – a decrease in tumor burden by more than 30 %, disease progression (PD) – an increase in the tumor burden by more than 20% or the appearance of new metastatic lesions. Objective response rate (ORR) was calculated as the percentage of subjects with CR and PR on treatment. The disease control rate (DCR) was the percentage of persons with CR, PR, and SD. Progression-free survival (PFS) was calculated as the difference between the date of registration of disease progression and the date of initiation of targeted therapy. Overall survival (OS) was calculated as the difference between the date of death from PD or another cause and the date of initiation of targeted therapy. After the PD was registered, telephone contact with patients was conducted every three months to assess their survival status. The follow-up period continued until the patient's death or the database lock date (June 01, 2024). In the case of loss of contact with the patient's relatives, data on the date of death were obtained from the cancer registry of the Sumy Regional Clinical Oncology Center.

Collection of information and its evaluation. Data on patients' age, sex, body mass index (BMI), smoking status, number of metastases and their localization, category T and category N, and the applied treatment regimen were obtained from primary medical records. The results of complete blood count tests and chemistry tests performed at most one week before starting targeted therapy with bevacizumab and TKI were used to calculate the inflammation indices. NLR, PLR, ALI, PNI, SII, and HALP were calculated for all patients. The NLR index was determined as the absolute number of neutrophils (ANC) / absolute number of lymphocytes (ALC), PLR – as platelets (g/l) / ALC, ALI – as BMI × albumin (g/l) / NLR, PNI – as albumin (g /l) + 0.005 × ALC, SII – as platelets (g/l) × ANC / ALC, HALP – as hemoglobin (g/l) × albumin (g/l) × ALC/platelets (g/l).

Statistical analysis. All data on patients' baseline clinicopathological characteristics and indicators of laboratory analyses were placed on the Exel platform. Statistical analysis was performed using the Stata V.18.0 software environment (StataCorp, Texas, USA; https://www.stata.com; 2024). Receiver operating characteristic (ROC) analysis was used to select the most sensitive and specific inflammation indices that can be potential predictors of the efficacy of targeted therapy and to determine cut-off values. Indices of inflammation whose area under the curve (AUC) was more significant than 0.5 were included for further investigation. The Kaplan-Meier method was used to estimate the PFS and OS. The significance of the difference between groups was established using the Log-rank test. Independent predictors of the efficacy of bevacizumab and TKI were determined by Cox regression analysis. Indicators were considered statistically significant at $P<0.05$.

RESULTS

Characteristics of patients. One hundred nine patients with mNSCLC who received bevacizumab or TKI therapy at the Sumy Regional Clinical Oncology Center participated in the study. The average age of the patients was 60 years (range 33–82). The studied cohort was mostly men (70.6%) and smokers (64.2%). Most patients had a BMI ≥25 (58.7%), less than three metastatic sites (67.9%), and received bevacizumab therapy (79.8%).

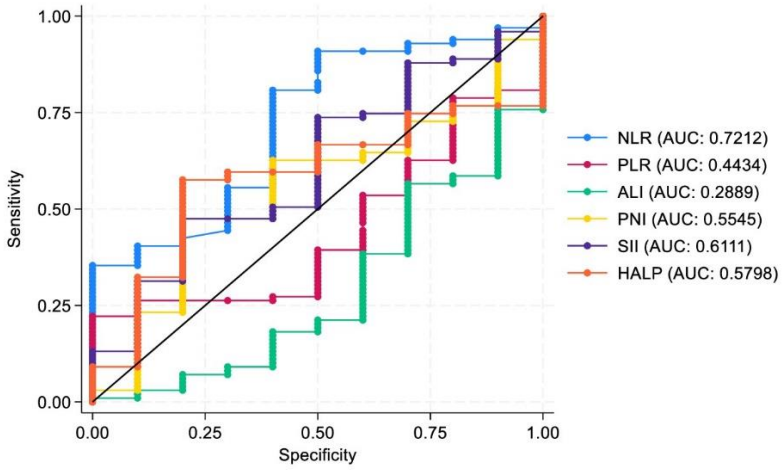

Figure 1 – Evaluation of NLR, PLR, ALI, PNI, SII, and HALP as predictors of the efficacy of bevacizumab and TKI therapy using ROC curves

Table 1 – Baseline clinicopathological characteristics of patients

Clinicopathological characteristics	Total number of patients (%), n=109
Age (years), n (%)	
Median	60
Range	33–82
<65	70 (64.2)
≥65	39 (35.8)
Sex, n (%)	
Female	32 (29.4)
Male	77 (70.6)
BMI	
<25	45 (42.3)
≥25	64 (58.7)
Smoking status, n (%)	
Never smokers	39 (35.8)
Current or former smokers	70 (64.2)
Number of metastases, n (%)	
<3	74 (67.9)
≥3	35 (32.1)
Metastases in the liver:	
Absent	83 (76.1)
Present	26 (23.9)
Metastases in the lung:	
Absent	45 (42.3)
Present	64 (58.7)
Metastases in the pleura:	
Absent	55 (50.5)
Present	54 (49.5)
Metastases in the bones:	
Absent	92 (84.4)
Present	17 (15.6)
Metastases in the kidneys:	
Absent	103 (94.5)
Present	6 (5.5)
Metastases in the brain:	
Absent	105 (96.3)
Present	4 (3.7)
Category T:	
1–2	56 (51.4)
3–4	53 (48.6)
Category N:	
0–1	34 (31.2)
2–3	75 (68.8)
Treatment regimen:	
Bevacizumab+chemotherapy	87 (79.8)
TKI	22 (20.2)
NLR	
≤2.84 (low)	43 (39.4)
>2.84 (high)	66 (60.6)
PNI	
≤40 (low)	75 (68.8)
>40 (high)	34 (31.2)
SII	
≤791.2 (low)	50 (45.9)
>791.2 (high)	59 (54.1)
HALP	
≤33.19 (low)	54 (49.5)
>33.19 (high)	55 (50.5)

The most sensitive and specific peripheral blood markers were NLR (AUC=0.7212, 95% confidence interval (CI) 0.63603–0.85633), PNI (AUC=0.5545, 95% CI 0.48608–0.65573), SII (AUC=0, 6111, 95% CI 0.52407–0.71572) and HALP (AUC=0.5798, 95% CI 0.494309–0.63201) (Fig. 1). ROC analysis determined that PLR and ALI are insufficiently sensitive and specific markers. Therefore, their influence on PFS and OS in mNSCLC patients who received bevacizumab and TKI therapy will not be evaluated. The cut-off values for NLR, PNI, SII, and HALP were determined to be 2.84, 40, 791.2, and 33.19, respectively. In more detail, the patient's baseline clinicopathological characteristics are summarized in Table 1.

The impact of inflammatory markers and patients' baseline clinicopathological characteristics on PFS. We found that among the studied markers of inflammation, only SII had a statistically significant effect on PFS. Patients with low SII had better PFS (Log-rank 0.0016). Median PFS in patients with low SII was 9.8 months versus 7.0 months in patients with high SII. NLR, PNI, and HALP did not show a difference in survival between patients with low and high levels of inflammatory markers (Log-rank P=0.0612, P=0.2970, P=0.2777, respectively). Therefore, SII statistically affects PFS in targeted therapy patients (Fig. 2).

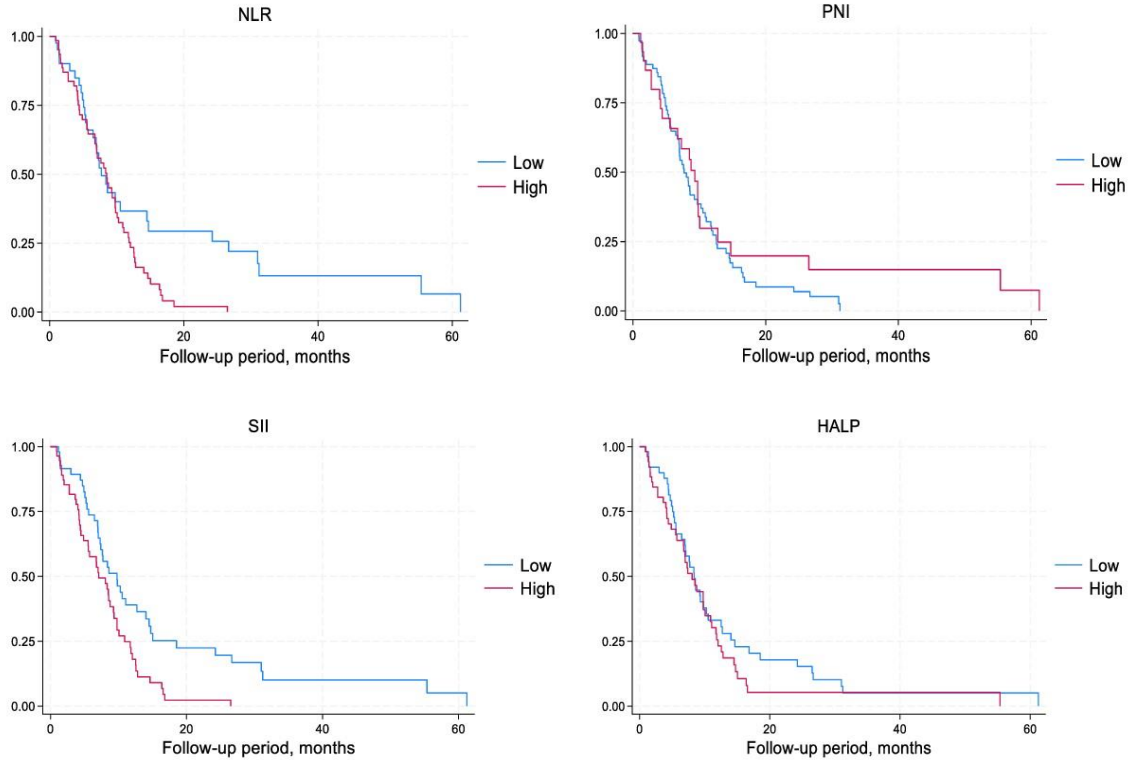

Figure 2 – Kaplan-Meier curves showing PFS according to NLR, PNI, SII, and HALP baseline levels

Multivariate Cox regression analysis was used to determine the prognostic impact of age, sex, BMI, smoking status, the number of metastases and their localization, category T and category N, and inflammatory markers on PFS in mNSCLC patients who received bevacizumab or TKI therapy. Smoking status (P=0.001), category N (P=0.034), and SII (P=0.018) can be considered as independent predictors of PFS. Patients with high SII, current or former smokers, and those whose category N is 2 or 3 have a lower PFS (Table 2).

The impact of inflammation markers and patients' baseline clinicopathological characteristics on OS. The correlation between inflammatory markers and OS was similar to that of PFS. A statistically significant relationship between SII and OS was registered (Log-rank P=0.0083). Patients with low SII have better OS. Median OS in patients with low SII was 13.9 months versus 9.1 months in patients with high SII. NLR, PNI, and HALP did not show a difference in OS between patients with low and high levels of inflammatory markers (Log-rank P=0.6159, P=0.5062, P=0.6927, respectively). Therefore, SII statistically significantly impacts on OS in targeted treated patients (Fig. 3).

Table 2 – Multivariate Cox regression analysis to assess the impact of clinicopathological characteristics and inflammatory markers on PFS

Clinicopathological characteristics	Hazard ratio	95% CI	P value
Age (<65 versus ≥65)	0.49	0.28–0.85	0.052
Sex (female versus male)	1.42	0.51–3.98	0.499
BMI (<25 versus ≥25)	1.09	0.63–1.86	0.747
Smoking status (never smokers versus current or former smokers)	3.20	1.64–6.23	0.001
Number of metastases (<3 versus ≥3)	0.49	0.23–1.03	0.062
Metastases in the liver (absent versus present)	1.61	0.85–3.05	0.142
Metastases in the lung (absent versus present)	1.43	0.78–2.62	0.237
Metastases in the pleura (absent versus present)	1.30	0.72–2.34	0.377
Metastases in the bones (absent versus present)	1.21	0.50–2.91	0.659
Metastases in the kidneys (absent versus present)	1.10	0.36–3.40	0.855
Metastases in the brain (absent versus present)	0.49	0.14–1.71	0.270
Category T (1–2 versus 3–4)	1.14	0.67–1.95	0.621
Category N (0–1 versus 2–3)	1.96	1.05–3.68	0.034
Treatment regimen (bevacizumab + chemotherapy versus TKI)	1.17	0.60–2.27	0.642
NLR (low versus high)	0.91	0.74–1.11	0.368
SII (low versus high)	1.00	1.00–1.02	0.018
PNI (low versus high)	1.94	0.88–1.01	0.145
HALP (low versus high)	0.98	0.95–1.00	0.103

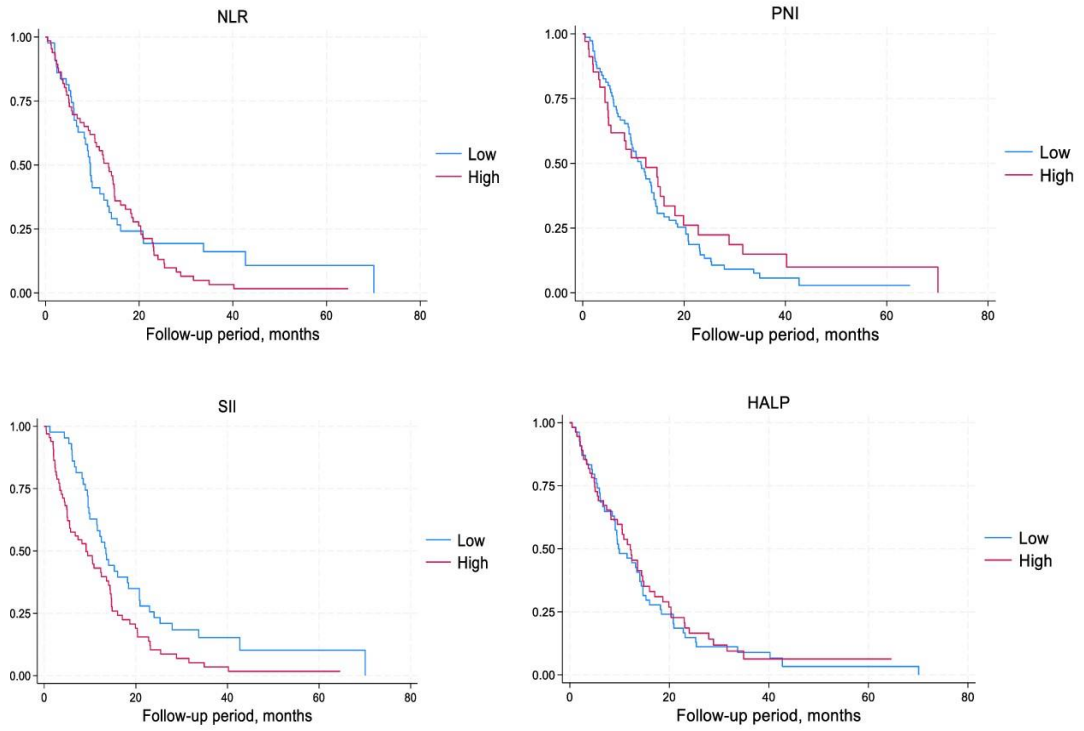

Figure 3 – Kaplan-Meier curves showing OS according to NLR, PNI, SII, and HALP baseline levels

Multivariate Cox regression analysis was used to determine the prognostic impact of age, sex, BMI, smoking status, the number of metastases and their localization, category T and category N, and inflammatory markers on OS in patients with mNSCLC who received bevacizumab or TKI. Smoking status (P=0.003), category N (P=0.018), and SII (P=0.006) can be considered as independent predictors of OS. Patients with high SII, current or former smokers, and those whose category N is 2 or 3 have a lower OS (Table 3).

Table 3 – Multivariate Cox regression analysis for assessing the impact of clinicopathological characteristics and inflammatory markers on OS

Clinicopathological characteristics	Hazard ratio	95% CI	P value
Age (<65 versus ≥65)	0.93	0.56–1.54	0.794
Sex (female versus male)	1.38	0.56–3.39	0.471
BMI (<25 versus ≥25)	0.87	0.52–1.44	0.594
Smoking status (never smokers versus current or former smokers)	2.38	1.33–4.26	0.003
Number of metastases (<3 versus ≥3)	0.69	0.34–1.40	0.315
Metastases in the liver (absent versus present)	1.16	0.62–2.18	0.631
Metastases in the lung (absent versus present)	0.76	0.45–1.28	0.316
Metastases in the pleura (absent versus present)	1.16	0.66–2.05	0.587
Metastases in the bones (absent versus present)	1.01	0.50–2.04	0.968
Metastases in the kidneys (absent versus present)	1.44	0.54–3.82	0.458
Metastases in the brain (absent versus present)	0.38	0.10–1.42	0.153
Category T (1–2 versus 3–4)	0.71	0.43–1.19	0.200
Category N (0–1 versus 2–3)	2.04	1.13–3.69	0.018
Treatment regimen (bevacizumab + chemotherapy versus TKI)	1.03	0.51–2.10	0.920
NLR (low versus high)	0.85	0.70–1.02	0.085
SII (low versus high)	1.00	1.00–1.01	0.006
PNI (low versus high)	0.93	0.88–1.37	0.052
HALP (low versus high)	0.99	0.98–1.01	0.954

Relationship between inflammatory markers, ORR, and DCR. On average, the follow-up period continued at 9.0 months (range 2 to 61 months). 87 (79.8%) patients had disease progression at the time of database lock, and 99 (90.8%) had death due to disease progression or any other causes. CR was not achieved in any patient. In 47 (43.1%), 42 (38.5%), and 20 (18.4%) patients, PR, SD, and PD were registered, respectively. The ORR was 43.1%, and the DCR was 81.6%.

After evaluating the DCR for the established independent predictors of the efficacy of bevacizumab and TKI therapy, it was confirmed that depending on the level of SII, patients have a different response to treatment. For patients with low SII, DCR was 93% versus 74.2% for patients with high SII (P=0.0198). Although there was a similar trend for the category N and smoking status, no statistically significant difference in treatment response was found. So, for patients with category N 0-1, DCR was 85.3% against 80% in persons with N 2–3 (P=0.5442). The DCR was 89.7% for never-smokers versus 77.1 for current or former smokers (P=0.1302).

DISCUSSION

We found that SII, category N, and smoking status are independent predictors of the efficacy of bevacizumab and TKI therapy affecting survival in mNSCLC patients. These factors are correlated with both PFS and OS. Multivariate analysis showed that patients with low SII, who had never smoked, and those whose category N was 0 or 1 had significantly better survival. Inflammatory markers ALI and PLR (AUC<0.5) were insufficiently sensitive and specific, so they were not evaluated regarding the impact on PFS and OS. NLR, PNI, and HALP lost their predictive value in the survival impact study phase and multivariable regression analysis. Nevertheless, SII showed a strong correlation with survival and response to treatment. DCR is statistically significantly higher in patients with low SII.

Inflammation plays an important role in the process of carcinogenesis and metastasis. The most available markers reflecting systemic inflammation are peripheral blood cells (lymphocytes, neutrophils, monocytes, platelets). The higher the number of

neutrophils, monocytes, and platelets, the lower the number of lymphocytes is associated with a worse prognosis [11, 12].

The mechanism of action of bevacizumab is related to the effect on vascular endothelial growth factor (VEGF), which is produced by tumor cells and pro-inflammatory blood cells. Hypoxia and inflammatory tumor microenvironment create a favorable environment for activating neutrophils and monocytes and stimulating VEGF synthesis [13, 14]. This leads to a violation of the differentiation and proliferation of antigen-presenting cells and the creation of an immunosuppressive environment. In addition, tumor-associated macrophages, myeloid suppressor cells, and regulatory T cells are activated [15]. All these cells can trigger alternative mechanisms of neoangiogenesis, resulting in resistance to bevacizumab [16]. For example, upregulation of VEGF-D (one of the four members of the VEGF family) causes resistance to bevacizumab [17].

Yang et al. [18] concluded that neutrophils play an important role in the development and progression of cancer, as well as neutrophil extracellular traps contribute to neoangiogenesis. In addition, neutrophilia leads to decreased albumin levels, activation of peritumoral aggregation of macrophages, and increased synthesis of IL-8, IL-6, and IL-1, which stimulates disease progression [19].

Unlike neutrophils, lymphocytes have antitumor activity. These peripheral blood cells suppress tumor cell proliferation and stimulate cytotoxic cell apoptosis. A lymphocyte decrease correlates with a poor response to anticancer therapy [20]. High levels of platelets and neutrophils combined with low levels of lymphocytes result in high SII and poor survival. All of the above explains why SII can be an independent predictor of the efficacy of bevacizumab or TKI therapy.

A high SII is considered a predictor of unfavorable prognosis of etoposide and cisplatin-based chemotherapy in small-cell lung cancer patients [21]. However, the predictive value of SII for chemoradiotherapy is quite the opposite. The higher the SII associated with the higher radiosensitivity and the better response to treatment [22]. Ju et al. [23] concluded that a low SII in EGFR-mutant lung adenocarcinoma patients was associated with better survival. Fang et al. [24] found that increased SII was associated with shorter PFS in mNSCLC patients receiving immunotherapy. The results of our study provide new evidence of the negative impact of high SII on survival in patients with mNSCLC receiving bevacizumab and TKI therapy.

In addition to SII, smoking status has a significant effect on survival. Current or former smokers lung cancer patients have lower PFS and OS [25]. Smoking has a cumulative effect, so the risk of lung cancer increases with the number of cigarettes used. The latent period preceding the appearance of cancer is about 10–30 years [26]. Recent studies confirm that smoking correlates with low survival, poor prognosis, high risk of lung cancer recurrence, and development of new malignancy. One of the reasons for the ineffectiveness of therapy is metabolic changes in the body of smokers, which can disrupt the pharmacodynamics and pharmacokinetics of drugs. Smoking cessation is considered an important request for the successful treatment of patients with lung cancer [27].

Multivariate regression analysis identified category N as an independent predictor of therapy efficacy and survival in mNSCLC patients treated with bevacizumab and TKI. Similar to our findings, Liang et al. [28] emphasize the impact of regional metastasis on long-term survival in NSCLC patients. Shih et al. [29] established that category N and extranodal extension can independently predict recurrence-free survival in patients with stage III NSCLC.

Although the obtained results are statistically reliable, our study has several limitations. First, the study was retrospective, so all data on infectious and autoimmune diseases were collected based on medical records. Secondly, changes in laboratory indicators could be related to taking medicines at home (for example, steroids), as a result of which this information was not reflected in the medical documentation and could in some way distort the obtained results.

CONCLUSIONS

SII is an independent predictor of the efficacy of bevacizumab or TKI therapy affecting PFS and OS in mNSCLC patients. A low SII correlates with better survival and favorable disease outcomes. In addition to SII, smoking status and category N are prognostic factors. Patients with mNSCLC who are current or former smokers and those whose category N is 2 or 3 have worse PFS and OS. The results indicate that systemic markers of inflammation are important for predicting disease outcomes and the efficacy of bevacizumab or TKI therapy.

AUTHOR CONTRIBUTIONS

Conceptualization O.V.; methodology O.V.; investigation O.V. and Y.M.; resources O.V.; data curation O.V.; writing—original draft preparation O.V.; writing—review and editing O.V. and Y.M.; visualization O.V.; supervision O.V.; project administration O.V.; funding acquisition O.V. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST

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