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BLOOD COUNT TEST FOR PREDICTING THE EFFICACY OF IMMUNE CHECKPOINT INHIBITORS

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Abstract. Identifying robust biomarkers to predict the efficacy of immune checkpoint inhibitors remains a key challenge in managing metastatic non-small cell lung cancer. This retrospective study aimed to investigate the prognostic and predictive value of complete blood count–derived inflammatory indices, in patients with metastatic non-small cell lung cancer receiving ICIs at the Sumy Regional Clinical Oncology Center between 2016 and 2024. A total of 105 patients were included, all of whom received either pembrolizumab or atezolizumab, with or without chemotherapy. Clinical data and baseline inflammatory indices were collected within seven days prior to treatment initiation. The indices analyzed included neutrophil-to-lymphocyte ratio (NLR), systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), and lymphocyte-to-monocyte ratio (LMR). Receiver operating characteristic analysis was employed to determine optimal cut-off values, which were 3.6 for NLR, 1.5 for SIRI, 926.0 for SII, and 3.3 for LMR. Progression-free survival and overall survival were evaluated using the Kaplan–Meier method, with comparisons performed via log-rank test. Multivariate Cox proportional hazards regression was used to assess independent prognostic factors. A p-value <0.05 was considered statistically significant.

The results demonstrated that among all analyzed markers, only NLR was significantly associated with overall survival. Patients with a low baseline NLR (<3.6) had a median overall survival of 19.7 months, compared to 10.0 months in those with high NLR (≥3.6), with a statistically significant difference (log-rank p=0.0191). Furthermore, multivariate Cox regression analysis confirmed NLR as an independent predictor of overall survival (HR=2.33, 95 % CI: 1.17–4.61, p=0.015). Other factors, including SII, SIRI, LMR, sex, therapy line, and treatment regimen, were not independently associated with survival outcomes. Although none of the inflammatory indices showed statistically significant impact on progression-free survival, a non-significant trend toward improved progression-free survival was noted in patients with low NLR (8.2 vs. 5.5 months, p=0.1084). In terms of treatment response, a significantly higher objective response rate was observed in the low NLR group (57.1 %) compared to the high NLR group (32.8 %, p=0.0213). Disease control rates, however, were comparable between the groups (85.7 % vs. 88.0 %, p=0.7515).

These findings highlight the potential utility of baseline NLR as a non-invasive, cost-effective biomarker for prognostication and response prediction in metastatic non-small cell lung cancer patients undergoing immunotherapy. In contrast, SIRI, SII, and LMR did not demonstrate prognostic significance in this cohort. While the study's retrospective and single-center nature limits external generalizability, the identification of NLR as an independent predictor of survival supports its integration into clinical workflows for early risk stratification. Further prospective, multicenter studies incorporating molecular and dynamic immunological parameters are warranted to validate and expand on these results.

Keywords: immune checkpoint inhibitors, prognosis, lung cancer, survival, NLR, inflammation indices.

Introduction. Over the past decade, the scientific community has focused its efforts on identifying biomarkers that would allow for predicting the efficacy of immunotherapeutic agents in oncology. Immune checkpoint inhibitors (ICIs) are increasingly being used to treat non-small cell lung cancer (NSCLC), particularly in the metastatic stages of the disease. The development of resistance to ICIs and the progression of NSCLC lead to fatal outcomes, highlighting the need to improve prediction methods in order to identify the category of patients who would derive the greatest benefit from immunotherapy [1].

Inflammation-related markers appear especially promising. Systemic inflammation manifests through qualitative and quantitative changes in the composition of immune cells localized in the tumor microenvironment and peripheral blood [2]. It has been observed that the effectiveness of ICIs largely depends on the patients' cytokine profile. High levels of tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), induced by the presence of an inflammatory tumor, stimulate myelopoiesis and lead to alterations in the composition of peripheral blood. In turn, platelets, lymphocytes, neutrophils, monocytes, and myeloid-derived suppressor cells release pro-inflammatory cytokines, including TGF-beta, IL-2, IL-6, IL-8, and interferon-gamma (IFN-γ), thereby increasing systemic inflammation [3].

The aim of the study: to assess the prognostic value of biomarkers derived from complete blood count in patients with metastatic NSCLC.

Approaches focused on evaluating the ratios of key blood cells offer significant advantages. First, they rely on data from complete blood count tests, which are routinely used in clinical practice. Second, these studies are inexpensive, accessible, minimally invasive, and have no contraindications. Third, calculating inflammation indices based on blood cell ratios requires no special skills or training [4].

To reflect the balance of immune cells and the state of the immune system, the most commonly used indices include the Systemic Immune-Inflammation Index (SII) [5], the Systemic Inflammation Response Index (SIRI) [6], the neutrophil-to-lymphocyte ratio (NLR), the platelet-to-lymphocyte ratio (PLR), and the lymphocyte-to-monocyte ratio (LMR) [7]. However, study results are

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not always consistent, as the prognostic value of inflammation indices largely depends on the tumor type, disease stage, treatment regimen, and the line of immunotherapy used.

Object and methods of research.

Patients and Study Design. This retrospective study included patients diagnosed with metastatic NSCLC who received treatment with ICIs at the Sumy Regional Clinical Oncology Center between 2016 and 2024. Eligible participants were aged 18 years or older and had received at least one therapeutic dose of an ICI, specifically atezolizumab or pembrolizumab. Patients with stage I, II, or III NSCLC, as well as those who had not received immunotherapy, were excluded from the study. Additional exclusion criteria included the presence of autoimmune diseases, infectious diseases, or febrile conditions within one month prior to the initiation of immunotherapy. Based on these inclusion and exclusion criteria, a total of 105 patients were enrolled in the final study cohort.

Ethical approval for this research was obtained from the Bioethics Committee for Experimental and Clinical Research of the Educational and Scientific Medical Institute at Sumy State University (Protocol No. 3/12, dated December 17, 2024). All patients who were alive at the time of enrollment provided written informed consent prior to participation.

Data Collection and Calculation of Inflammatory Indices. Clinical data, including patient sex, immunotherapeutic regimens, and lines of therapy, were extracted from medical records. Inflammatory indices were calculated using results from complete blood count tests performed no more than seven days before the administration of the first ICI dose. The following indices were computed: the Systemic Inflammation Response Index (SIRI), calculated as neutrophils × monocytes / lymphocytes; the Systemic Immune-Inflammation Index (SII), as platelets ($\times 10^9$/L) × neutrophils / lymphocytes; the neutrophil-to-lymphocyte ratio (NLR), as neutrophils / lymphocytes; the platelet-to-lymphocyte ratio (PLR), as platelets ($\times 10^9$/L) / lymphocytes; the lymphocyte-to-monocyte ratio (LMR), as lymphocytes / monocytes; and the monocyte-to-lymphocyte ratio (MLR), as monocytes / lymphocytes.

Assessment of Treatment Response. Treatment response was monitored using computed tomography scans, which were performed every 2–3 cycles of therapy. Radiological assessment of tumor response followed the immune Response Evaluation Criteria in Solid Tumors (iRECIST), which classify outcomes as progressive disease (PD), stable disease (SD), partial response (PR), or complete response (CR). The disease control rate (DCR) was defined as the proportion of patients achieving SD, PR, or CR, while the objective response rate (ORR) was defined as the proportion achieving PR or CR. Progression-free survival (PFS) was calculated from the date of the first ICI dose to the date of documented disease progression, and overall survival (OS) was calculated from the first ICI dose to the date of death. Mortality data were obtained via telephone follow-up with relatives and from the cancer registry database of the Sumy Regional Clinical Oncology Center.

Statistical Analysis. Statistical analysis was performed using Stata software, version 18.0. Continuous variables were expressed as numerical values and percentages. Receiver operating characteristic (ROC) curve analysis was used to determine the area under the curve (AUC) and optimal cut-off values for the most sensitive inflammatory indices, which were established as follows: 1.5 for SIRI, 926.0 for SII, 3.6 for NLR, and 3.3 for LMR. Median PFS and OS were estimated using the Kaplan–Meier method. Differences in survival between patient subgroups with low versus high inflammatory indices were evaluated using the log-rank test. Prognostic factors associated with survival were assessed using multivariate Cox proportional hazards regression modeling. A p-value of less than 0.05 was considered statistically significant.

Research results and their discussion.

Clinical and Laboratory Characteristics of Patients

The final study cohort consisted of 105 patients diagnosed with metastatic non-small cell lung cancer. Among them, 89 patients (84.8 %) were male, and 16 (15.2 %) were female. The majority of patients received immunotherapy as a first-line treatment option. Specifically, 77.1 % of patients began therapy with ICIs as part of their initial treatment regimen, and most of them (63.8 %) were treated with a combination of an ICIs and chemotherapy.

To evaluate the potential predictive value of systemic inflammation in the context of immunotherapy, several inflammation-related indices were analyzed. Among them, the SIRI, SII, NLR, and LMR demonstrated acceptable specificity and sensitivity. The AUC for each of these markers was calculated using ROC analysis, yielding the following results: for SIRI, the AUC was 0.5439 (95 % confidence interval [CI]: 0.30544–0.78228); for SII, 0.5380 (95 % CI: 0.28727–0.78876); for NLR, 0.5497 (95 % CI: 0.30643–0.79299); and for LMR, 0.5637 (95 % CI: 0.37821–0.74928). These values suggest a moderate prognostic potential of the aforementioned indices.

In contrast, both the PLR and MLR demonstrated AUC values below 0.5, indicating low diagnostic performance and limited prognostic value in this patient population (Fig. 1). As a result, these two indices were excluded from further analyses regarding treatment efficacy. A summary of the patients' baseline demographic data, clinical characteristics, and laboratory parameters is provided in Table 1.

Impact of Inflammatory Indices on Survival and Efficacy of Immune Checkpoint Inhibitor Therapy. The analysis revealed that none of the evaluated inflammatory indices had a statistically significant effect on PFS. The median PFS did not significantly differ between patients with low and high levels of SIRI, SII, and LMR, with log-rank p-values of 0.7353, 0.5683, and 0.7571, respectively. However, a trend toward improved PFS was observed in patients with lower NLR values. Specifically, patients with low NLR had a median PFS of 8.2 months, compared to 5.5 months in those with high NLR, although this difference did not reach statistical significance (log-rank p = 0.1084; Figure 2).

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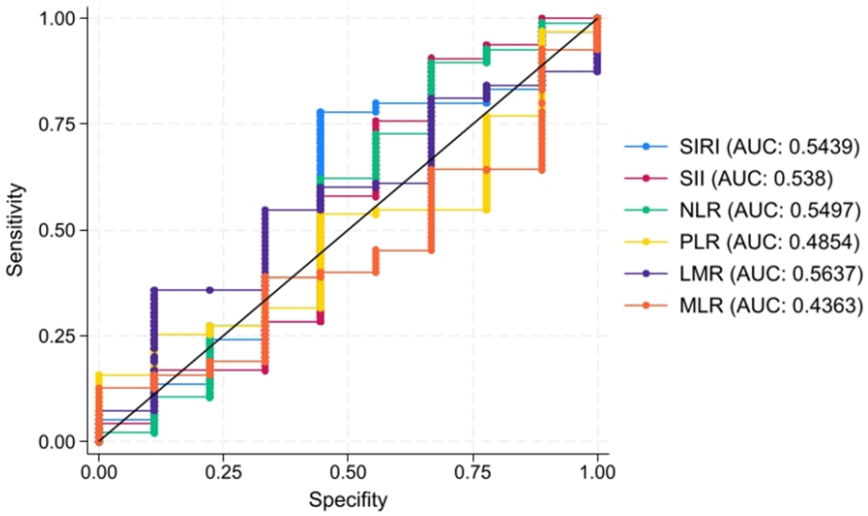

Fig. 1. Evaluation of the specificity and sensitivity of SIRI, SII, NLR, PLR, LMR, and MLR for predicting the effectiveness of ICI

Table 1

Clinical and laboratory characteristics of the studied cohort

Variables		Total number of patients, n=105
Sex, n (%)	Female	16 (15.2)
	Male	89 (84.8)
Immunotherapy regimen, n (%)	ICIs monotherapy	38 (36.2)
	Chemoimmunotherapy	67 (63.8)
Treatment lines, n (%)	First	81 (77.1)
	Second	24 (22.9)
SIRI, n (%)	<1.5 (low)	53 (50.5)
	≥1.5 (high)	52 (49.5)
SII, n (%)	<926.0 (low)	57 (54.3)
	≥926.0 (high)	48 (45.7)
NLR, n (%)	<3.6 (low)	63 (60.0)
	≥3.6 (high)	42 (40.0)
LMR, n (%)	<3.3 (low)	48 (45.7)
	≥3.3 (high)	57 (54.3)

In terms of OS, a statistically significant difference was observed based on NLR levels. Patients with low NLR exhibited a notably longer median OS of 19.7 months, in contrast to 10.0 months among patients with high NLR (log-rank p = 0.0191). Conversely, OS was comparable between groups stratified by SIRI, SII, and LMR, with log-rank p-values of 0.9694, 0.4688, and 0.9490, respectively (Figure 3).

These findings suggest that among the analyzed inflammatory biomarkers, only NLR demonstrated a significant prognostic value for overall survival in patients with metastatic NSCLC undergoing treatment with ICIs.

In the analyzed cohort, the ORR and DCR were 51.4 % and 86.6 %, respectively. A statistically significant difference in ORR was observed between patients with low and high NLR values. Specifically, 57.1 % of patients with low NLR achieved an objective response, compared to only 32.8 % of those with high NLR (p = 0.0213). In contrast, no significant difference was found in DCR between the low and high NLR groups, with rates of 85.7 % and 88.0 %, respectively (p = 0.7515). These findings suggest that a lower NLR may be associated with better immunotherapeutic efficacy, potentially reflecting a more favorable balance between neutrophils and lymphocytes in the immune microenvironment.

Identification of independent survival predictors. To identify independent predictors of PFS and OS, a multivariate Cox regression analysis was performed. The results demonstrated that NLR was an independent prognostic factor for OS. Patients with a hight NLR had significantly poorer survival outcomes compared to those with a low NLR (hazard ratio [HR] = 2.33, 95 % CI: 1.17–4.61, p = 0.015). Other clinical and laboratory variables – including sex, line of therapy, immunotherapeutic regimen, as well as SIRI, SII, and LMR – did not show significant prognostic value in the multivariate model (Table 2).

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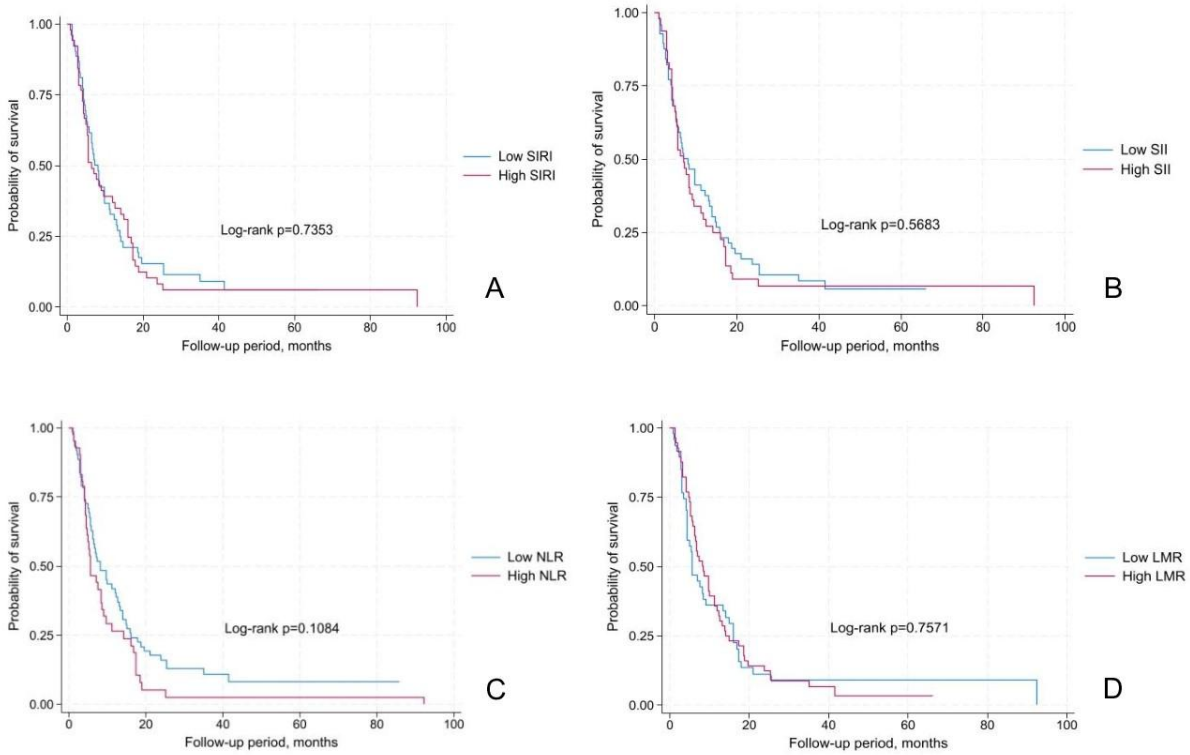

Fig. 2. Progression-free survival curves based on baseline SIRI (A), SII (B), NLR (C), and LMR (D)

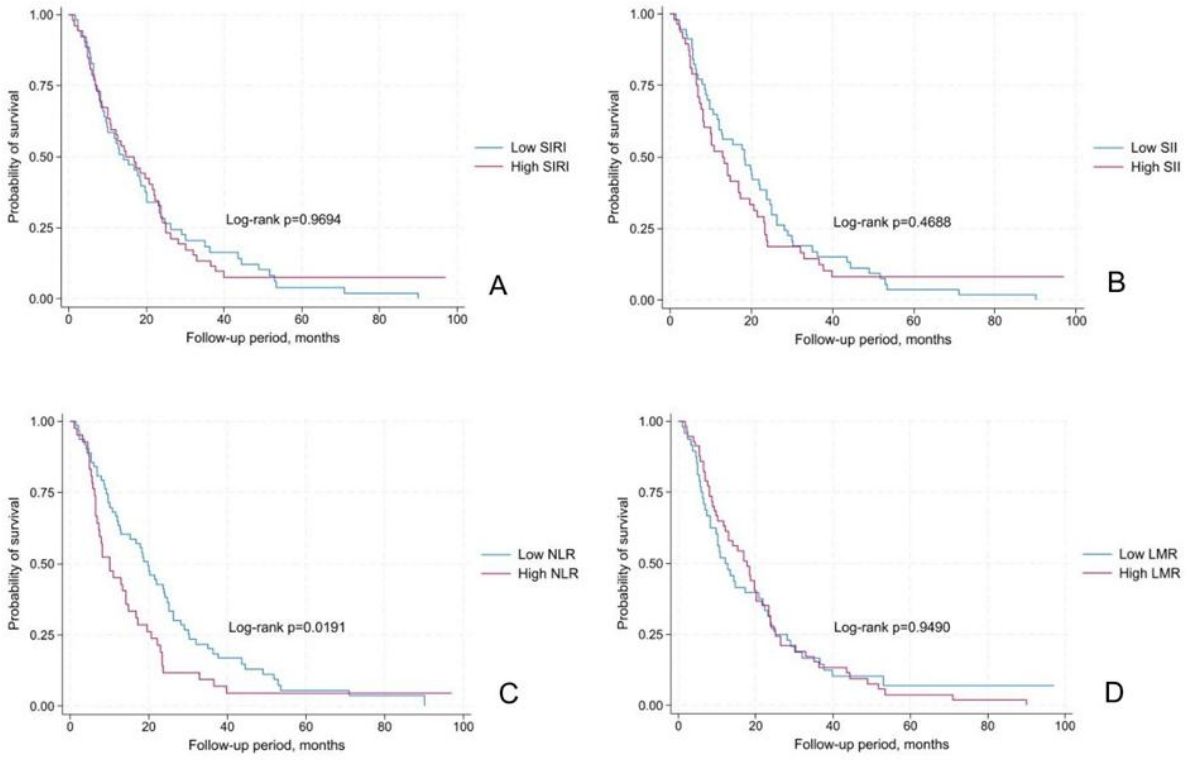

Fig. 3. Overall survival curves based on baseline SIRI (A), SII (B), NLR (C), and LMR (D)

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Table 2

Cox proportional hazards model for predicting survival in patients receiving ICI

Variables	PFS			OS		
	HR	95 % CI	p	HR	95 % CI	p
Sex (male versus female)	1,30	0,74–2,28	0,358	1,39	0,77–2,51	0,263
Treatment line (first versus second)	0,75	0,33–1,67	0,483	0,92	0,42–1,98	0,837
Immunotherapy regimen (ICI monotherapy versus chemo-immunotherapy)	0,80	0,49–1,30	0,380	0,93	0,58–1,50	0,792
SIRI (low versus high)	0,97	0,81–2,30	0,929	0,81	0,42–1,56	0,539
SII (low versus high)	0,75	0,37–1,52	0,437	0,73	0,35–1,53	0,414
NLR (low versus high)	1,80	0,92–3,54	0,085	2,33	1,17–4,61	0,015
LMR (low versus high)	1,00	0,57–1,77	0,977	0,99	0,55–1,76	0,981

In the present study, we observed the relationship between the NLR, survival outcomes, and response to ICI therapy in patients with metastatic NSCLC. Our results indicate that a low baseline NLR is significantly associated with improved OS and a higher ORR, and NLR was confirmed as an independent predictor of OS in multivariate analysis.

NLR is among the most widely studied and easily accessible systemic inflammatory biomarkers derived from routine complete blood count. Its prognostic value in NSCLC has been supported by multiple studies and meta-analyses. Elevated NLR likely reflects a pro-inflammatory tumor microenvironment dominated by neutrophils, which are known to promote angiogenesis, tumor cell proliferation, and immune evasion via the release of biologically active factors such as hepatocyte growth factor, epidermal growth factor, and platelet-derived growth factor [8, 9].

Our findings are consistent with previous studies, including Peng et al. [9], who demonstrated that NLR <5 was associated with better survival and response rates in patients treated with PD-1 inhibitors. A systematic review by Platini et al. [10] and studies by Pu et al. [11] and Smorodska et al. [12] similarly concluded that elevated NLR is a negative prognostic factor in advanced NSCLC.

In addition to earlier evidence, recent data from Zhang et al. [13] confirm that baseline NLR and SII are predictive of immunotherapy outcomes in advanced NSCLC, with lower values correlating with better survival. Importantly, Zheng et al. [14] found that patients with PD-L1 ≥50 % expression and low NLR exhibited significantly deeper responses to first-line ICI monotherapy, suggesting that systemic inflammatory status may influence tumor responsiveness even in cases with high PD-L1 expression.

He et al. [15] expanded this understanding by demonstrating the prognostic role of SII and other inflammatory markers in lung cancer patients with bone metastases – a population typically associated with poorer outcomes. Our study did not find SII, SIRI, or LMR to be statistically significant predictors of OS or PFS; however, it is possible that their role may vary depending on disease burden, metastatic pattern, or therapy type.

The clinical significance of these findings lies in the utility of NLR as a non-invasive, low-cost, and readily available biomarker for early stratification of patients undergoing immunotherapy. Lei et al. [16] emphasized that NLR, PLR, and SII/albumin ratio all correlate with immunotherapy outcomes and may reflect not only tumor biology but also systemic immunonutritional status, which influences treatment tolerance and efficacy. Furthermore, Yuan et al. [17] demonstrated that combining inflammatory markers with deep learning models enhances early prediction of immunotherapy response in unresectable NSCLC, highlighting opportunities for integrating NLR into AI-assisted clinical decision-making tools.

Katayama et al. [18] evaluated inflammatory markers in patients receiving atezolizumab monotherapy and confirmed that low baseline NLR was significantly associated with longer survival. Similarly, Zhu et al. [19] demonstrated the diagnostic potential of NLR and PLR in distinguishing lung cancer patients from healthy individuals, further emphasizing the immunologic relevance of these indices.

Despite widespread agreement on the prognostic role of NLR, there remains no consensus on the optimal cut-off value. In our study, a threshold of 3.6 was determined via ROC analysis. Other studies have reported cut-offs ranging from 2.8 to 5, depending on methodology, population, and endpoint [20–22]. A commonly used value across various studies is 4, which may serve as a practical benchmark in routine practice.

This study has several limitations. First, its retrospective and single-center design may introduce selection bias and limits generalizability. Second, we did not evaluate key tumor-specific factors such as PD-L1 expression, tumor mutational burden, or EGFR/ALK mutation status, which could confound survival outcomes. Third, dynamic changes in NLR during treatment – potentially more informative than baseline values – were not assessed.

Nevertheless, the results of this study have important clinical implications. NLR could serve as an adjunctive biomarker in immunotherapy decision-making. Moreover, its simplicity allows for repeated, real-time monitoring during treatment, providing clinicians with a low-cost tool for adaptive management. The identification of NLR as an independent predictor of OS highlights its potential role not only in prognostication but also in optimizing patient selection for ICIs.

Conclusions:

1. A low baseline neutrophil-to-lymphocyte ratio in patients with metastatic NSCLC was associated with significantly improved overall survival. The median overall survival was 19.7 months in patients with low NLR compared to 10.0 months in those with high NLR (log-rank p = 0.0191).

2. No significant differences in overall survival were observed between patients with low and high values of other inflammatory indices, including SIRI, SII, and

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LMR (log-rank p = 0.9694, p = 0.4688, and p = 0.9490, respectively), indicating that these markers lacked prognostic value in this cohort.

3. Multivariate Cox regression analysis identified low NLR as an independent predictor of overall survival in patients with metastatic NSCLC (HR = 2.33; 95 % CI: 1.17–4.61; p = 0.015).

4. Patients with low NLR demonstrated significantly better objective response to immune checkpoint inhibitor therapy compared to those with high NLR (57.1 % vs. 32.8 %; p = 0.0213), supporting the association between this inflammatory index and immunotherapy efficacy.

Prospects for further research. We are going to investigate the prognostic significance of the tumor microenvironment in the effectiveness of immunotherapy in patients with metastatic non-small cell lung cancer.

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Conflict of interest: absent.

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КЛІНІЧНИЙ АНАЛІЗ КРОВІ ДЛЯ ПРОГНОЗУВАННЯ ЕФЕКТИВНОСТІ ІНГІБІТОРІВ ІМУННИХ КОНТРОЛЬНИХ ТОЧОК

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Резюме. Визначення надійних біомаркерів для прогнозування ефективності імунотерапії залишається актуальним завданням у лікуванні метастатичного недрібноклітинного раку легень. У цьому ретроспективному дослідженні проаналізовано прогностичну та предиктивну цінність індексів запалення, розрахованих на основі клінічного аналізу крові у 105 пацієнтів із метастатичним недрібноклітинним раком легень, які отримували інгібітори імунних контрольних точок у Сумському обласному клінічному онкологічному центрі в 2016–2024 роках. Усі пацієнти отримували пембролізумаб або атезолізумаб з хіміотерапією або без неї. Вихідні показники визначали до початку терапії. Аналізували індекси: NLR, SII, SIRI, LMR. Оптимальні порогові значення визначали методом ROC-аналізу: 3,6 для NLR, 1,5 для SIRI, 926,0 для SII, 3,3 для LMR. Виживаність без прогресування та загальну виживаність оцінювали методом Каплана–Майєра, порівняння проводили логранговим тестом. Прогностичні фактори визначали за допомогою регресійної моделі Кокса. Статистично значущими вважали $p<0,05$. Єдиним індексом, який достовірно асоціювався із загальною виживаністю, був NLR. Пацієнти з низьким NLR (<3,6) мали медіану загальної виживаності 19,7 міс проти 10,0 міс у пацієнтів із високим NLR ($p=0,0191$). У моделі Кокса NLR залишався незалежним прогностичним фактором загальної виживаності (HR=2,33; 95 % ДІ: 1,17–4,61; $p=0,015$). Інші індекси (SII, SIRI, LMR), стать, режим і лінія терапії не впливали на загальну виживаність. На її прогресування індекси не мали достовірного впливу, проте для NLR спостерігалась позитивна тенденція (8,2 vs 5,5 міс; $p=0,1084$). Частота об'єктивної відповіді на лікування була достовірно вищою при низькому NLR (57,1 % проти 32,8 %; $p=0,0213$). Рівень контролю над захворюванням не відрізнявся. Таким чином, базовий NLR можна вважати доступним, неінвазивним біомаркером прогнозу та відповіді на інгібітори імунних контрольних точок у хворих на метастатичний недрібноклітинний рак легень.

Ключові слова: інгібітори імунних контрольних точок, прогноз, рак легень, виживання, NLR, індекси запалення.

Конфлікт інтересів: відсутній.

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