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Unlocking the potential: the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) as biomarkers informing immunotherapy outcomes in lung cancer patients — single oncology center experience and literature review

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ABSTRACT

Introduction. The neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR), two promising biomarkers of effectiveness of cancer immunotherapy, have obtained great attention in recent years. The NLR and PLR are both simple and readily available markers derived from routine blood tests. It is postulated that integrating these biomarkers into clinical practice could facilitate monitoring immunotherapy effects.

In this study, we retrospectively examined NLR and PLR values in non-small cell lung cancer patients (NSCLC) receiving second-line immunotherapy.

Material and methods. The study group included 73 NSCLC patients: 38 men and 35 women. Twenty-three patients were diagnosed with squamous cell carcinoma (SqCC), and 50 patients with non-squamous cell carcinoma (non-SqCC). We assessed NLR and PLR values at immunotherapy initiation (NLR1, PLR1) and after 3 months of the follow-up (NLR2 and PLR2). These parameters were correlated with the clinical characteristics of patients, response to treatment, progression-free survival (PFS), and overall survival (OS).

Results. The values of PLR1 and delta PLR were significantly higher in non-SqCC patients compared to SqCC patients. Other clinical and demographic factors did not influence the values of NLR1, NLR2, PLR2, or delta NLR. Medians of NLR1 and NLR2 were significantly lower in patients with controlled disease than in patients with disease progression. Patients with PFS longer than 12 months had a significantly lower median NLR2 than patients with PFS shorter than 1 year. A factor that significantly increased the risk of progression and death was a high NLR2 value.

Conclusions. NLR and PLR represent promising biomarkers for monitoring immunotherapy effectiveness in cancer patients, which offer insights into the dynamic interplay between the host immune system and tumor biology. Further research is warranted to validate their utility in larger patient cohorts and standardize their incorporation into clinical practice.

Keywords: non-small cell lung cancer, predictive factors, immunotherapy, neutrophils-to-lymphocytes ratio, platelet-to-lymphocyte ratio

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Introduction

Predictive factors play a crucial role in the determination of prognosis and treatment outcomes for non-small cell lung cancer (NSCLC) patients. These factors are used for proper qualification of lung cancer patients to an appropriate treatment regimen [1, 2]. In NSCLC treatment, expression of programmed death ligand 1 (PD-L1) on tumor cells (TC) emerges as a vital predictive marker that influences patient response to immunotherapy. Programmed death ligand 1, found on the surface of tumor cells, plays a critical role in lowering the immune system's ability to recognize and attack cancer cells by interacting with its receptor — programmed death 1 (PD-1) on T cells [2, 3]. High PD-L1 expression within tumor tissues is indicative of a suppressed immune response and it has been associated with enhanced sensitivity to immune checkpoint inhibitors (ICIs) targeting this pathway. Consequently, evaluation of PD-L1 expression on TC *via* immunohistochemistry (IHC) assists clinicians in stratifying patients for immunotherapy or chemoimmunotherapy, aiding in treatment decision-making and ultimately improving therapeutic outcomes [2–4].

Programmed death ligand 1, although widely used in the qualification for immunotherapy, is an imperfect marker, as some NSCLC patients with low or absent PD-L1 expression still respond positively to treatment [4, 5]. Additionally, PD-L1 expression can vary over time and may differ between primary tumors and metastatic lesions, and even within the same tumor [5]. These limitations underscore the importance of continued research to identify novel biomarkers that can complement or surpass PD-L1 in predicting immunotherapy response, ultimately improving patient qualification and treatment efficacy in lung cancer management. These factors should be easily assayed and readily available in all patients.

Among other factors, two emerging biomarkers, the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR), have garnered significant attention in recent years [6]. The NLR and PLR are both simple and readily available markers derived from routine blood tests. Elevated levels of the NLR and PLR have been associated with systemic inflammation and poor prognosis in various cancers, including NSCLC [7]. Studies have suggested that a high NLR and PLR correlate with advanced tumor stage, larger tumor size, lymph node involvement, and presence of metastases in NSCLC patients. Furthermore, elevated NLRs and PLRs have been linked to decreased overall survival (OS) and poorer response to chemotherapy and immunotherapy in NSCLC patients [6–8].

In this study, we retrospectively examined the NLR and PLR values in non-small cell lung cancer patients receiving second-line immunotherapy. We assessed the value of these parameters at the time of immunotherapy initiation (NLR1, PLR1), at the clinical follow-up after 3 months (NLR2, PLR2), and assessed the changes in these parameters. We speculated that integrating these biomarkers into clinical practice could facilitate the monitoring of immunotherapy effectiveness, and disease progression could be suspected early before the use of imaging tests. Moreover, these parameters could be useful as predictive factors for immunotherapy qualification. However, further research is needed to validate the utility of the NLR and PLR and to elucidate their underlying mechanisms in tumor progression and treatment response.

Material and methods

Study population

The study group included 73 NSCLC patients (median age 66 ± 6.88 years), including 38 men (52.05%) and 35 women (47.95%). Squamous cell carcinoma (SqCC) was diagnosed in 23 patients (31.5%) and non-squamous cell carcinoma (non-SqCC) in 50 patients (68.5%). Twenty-seven patients (37%) were under 65 years, and 46 patients (63%) were older than 65 years. Sixty-eight patients were former or current smokers and all patients were in good or very good performance status according to the Eastern Cooperative Oncology Group — the World Health Organization (ECOG-WHO) scale. Programmed death ligand 1 expression on tumor cells was determined in 52 patients (71.2%), 16 of whom (30.8%) did not express this molecule on TC. Mutations in the *EGFR* gene and *ALK* gene rearrangements were excluded in all patients. In the second line of treatment, 27 patients (37%) received nivolumab and 46 (63%) patients received atezolizumab. 8 patients (10.9%) are still receiving immunotherapy and 19 patients (26%) remain alive during follow-up. The median follow-up time was 14.3 months (patients were observed from March 2017 to October 2023). In all patients, the response to treatment and progression-free survival (PFS) were assessed based on Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Overall survival was measured from the initiation of second-line immunotherapy to death or last follow-up.

Neutrophil-to-lymphocyte (NLR) and platelet-to-lymphocyte ratio (PLR) calculation

The NLR and PLR were calculated as the ratio of neutrophil count to lymphocyte count and as the ratio of platelet count to lymphocyte count, respectively. The NLR and PLR were calculated before immunotherapy (NLR1 and PLR1) and at the first follow-up

approximately 3 months after treatment initiation (NLR2 and PLR2). The difference between the first and the second measurement of these indicators was also calculated (delta NLR and delta PLR).

Statistical analysis

Statistical analysis was performed using Statistica 13.3 (TIBCO Software Inc, Palo Alto, US) and MedCalc (MedCalc Software Ltd, Ostend Belgium) software. The U-Mann-Whitney test was used to assess differences in NLR and PLR values in groups differing in clinical factors, response to treatment, duration of PFS and OS. The Wilcoxon matched pairs test was used to compare the median NLR or PLR calculated before and during immunotherapy. Kaplan-Meier survival and multiparameter Cox regression analyses were used for the calculation of the risk of progression or death in different groups of patients. The results were presented as medians, standard deviations, maximum and minimum values (min–max), and 95% confidence intervals (CI). A p-value below 0.05 was considered statistically significant.

Results

The values of the PLR1 ($p = 0.01307$) and delta PLR ($p = 0.0404$) were significantly higher in patients with non-SqCC compared to patients with SqCC. Other clinical parameters did not influence the value of PLR1. Clinical and demographic factors did not influence the value of NLR1, NLR2, PLR2, and delta NLR. The median PLR1 (mPLR1) was significantly higher ($p = 0.01432$) than the median PLR2 (mPLR2). These medians were 245.1 and 218, respectively (Fig. 1). However, the medians of NLR1 (mNLR1 = 4.35) and NLR2 (mNLR2 = 3.95) were not significantly different.

Partial response occurred in 18 patients, disease stabilization in 33 patients, and disease progression in 22 patients. Median PFS (mPFS) was 6.33 months (95% CI 4.87–9.2) and median OS (mOS) was 17.6 months (95% CI 12.72–24.73). Twenty-two patients survived without progression for more than 12 months. One-year OS was recorded in 32 patients.

Relationship between NLR or PLR and response to treatment

Medians of NLR1 and NLR2 were significantly lower ($p = 0.00975$ and $p = 0.000359$, respectively) in patients with disease control [partial response (PR) and stable disease (SD)] than in patients with disease progression. These medians were 3.96 *vs.* 6.49 for NLR1 and 3.67 *vs.* 6.59 for NLR2 (Fig. 2).

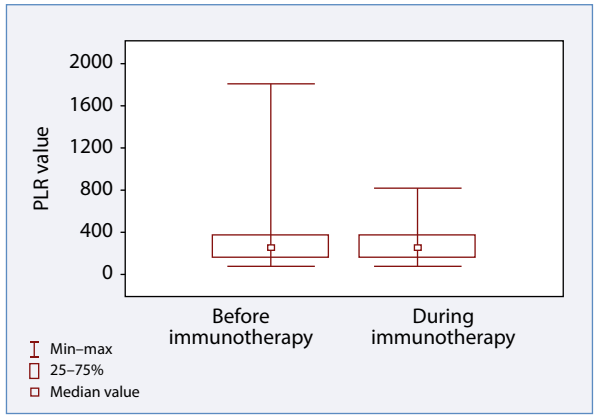

Figure 1. Differences in platelet-to-lymphocyte ratio (PLR) values (PLR 1 *vs.* PLR 2) before and during second-line immunotherapy in non-small cell lung cancer (NSCLC) patients (mPLR1 = 245.1, mPLR2 = 218; $p < 0.05$)

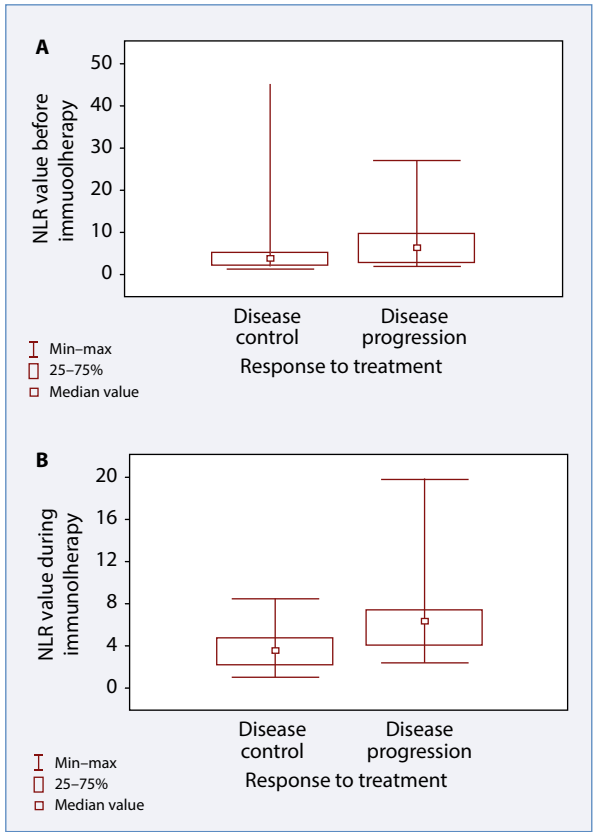

Figure 2. Differences in neutrophil-to-lymphocyte ratio (NLR) 1 (**A**) and NLR 2 (**B**) values depending on response to second-line immunotherapy in non-small cell lung cancer (NSCLC) patients (mNLR1 = 3.96 *vs.* 6.49, $p = 0.00975$, mNLR2 = 3.67 *vs.* 6.59; $p = 0.000359$)

Platelet-to-lymphocyte ratio 1, PLR2, delta NLR, and delta PLR were similar in patients with disease control in comparison to patients with disease progression.

Progression-free survival

Patients with PFS longer than 12 months had a significantly (p = 0.01515) lower median NLR2 than patients with PFS shorter than 1 year (3.65 *vs*. 4.93; Fig. 3). Neutrophil-to-lymphocyte ratio 1, PLR1, PLR2, delta NLR, and delta PLR did not differ between the study groups.

In an univariate analysis, the risk of progression did not depend on the age, sex pathological diagnosis, cigarette smoking status, type of immunotherapy, percentage of TC with PD-L1 expression, NLR1, PLR1, PLR2, delta NLR or delta PLR values. The factor that significantly increased the risk of progression (HR = 2.1766; 95% CI 1.284–3.6897; p = 0.0039) was a high NLR2 value (Fig. 4). Median PFS in patients with NLR values above the median was 5.93 (95% CI 2.73–9.2) months, and in patients with NLR values below the median — 6.53 (95% CI 5.63–24.03) months. In the multivariate analysis, the only factor significantly increasing (overall model fit: χ^2 = 8.023; p = 0.0046) the risk of progression was a high NLR2 value (HR = 2.1055; 95% CI 1.2537–3.536).

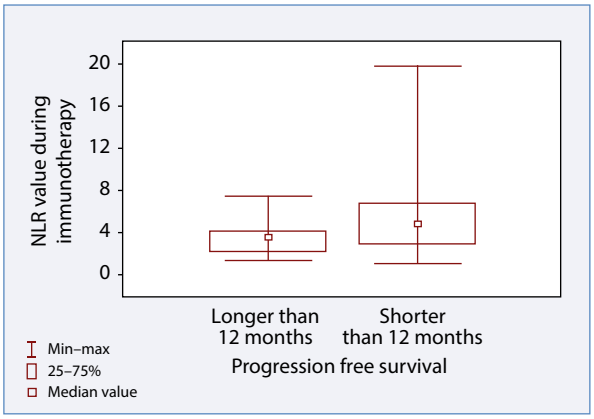

Figure 3. Neutrophil-to-lymphocyte ratio (NLR) 2 values in non-small cell lung cancer (NSCLC) patients with short and long progression-free survival (mNLR2 = 3.65 *vs.* 4.93; p = 0.01515)

Overall survival

Patients with OS longer than 1 year had a significantly (p = 0.00294) lower median NLR2 than patients with OS shorter than 1 year (3.66 *vs*. 5.87; Fig. 5). Neutrophil-to-lymphocyte ratio 1, PLR1, PLR2, delta NLR, and delta PLR did not differ between the study groups.

In a univariate analysis, the risk of death did not depend on the age, sex, cigarette smoking status, type of immunotherapy, percentage of TC with PD-L1 expression, NLR1, PLR1, PLR2, and delta PLR values. Patients with SqCC had a significantly higher (HR = 1.9753; 95% CI 1.0641–3.6669) risk of death than patients with non-SqCC. Median OS in these groups was 10.57 (95% CI 6.2–14.33) months and 24.73 (95% CI 17.6–29.5) months, respectively. Moreover, one factor that significantly increased the risk of death (HR = 2.2759; 95% CI 1.2805–4.0451; p = 0,0051) was a high NLR2 value (Fig. 6). Median OS in patients with an NLR2 value above the median was 11.97 months (95% CI 5.90–23.57) and in patients with an NLR2 value below the median — 22.87 months (95% CI 15.73–36.6). Patients

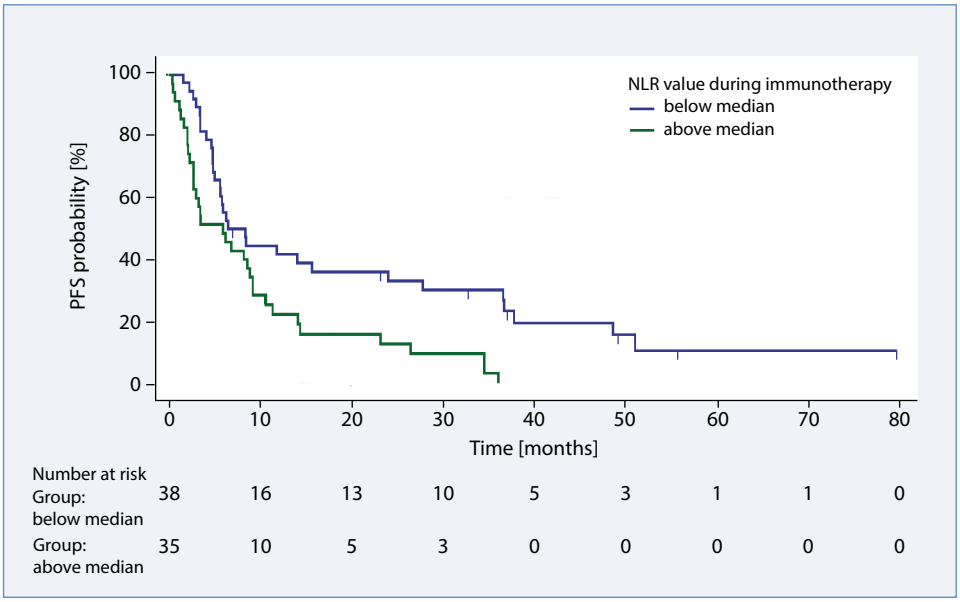

Figure 4. Risk of progression in non-small cell lung cancer (NSCLC) patients with neutrophil-to-lymphocyte ratio (NLR) 2 value below and above the median [hazard ratio (HR) = 2.1766; 95% confidence interval (CI) 1.284–3.6897; p = 0.0039]

who did not have a high reduction in the NLR during immunotherapy (delta NLR below the median) had a significantly higher risk of death (HR = 1.7699; 95% CI 1.0254–3.0551; p = 0.0404) than patients with a high reduction in the NLR (delta NLR above the median). Median OS in these groups of patients was: 14.33 (95% CI 10.57–17.9) months and 28.4 (95% CI 13.43–36.93) months, respectively (Fig. 7).

In the multivariate analysis, the factor that significantly increased (overall model fit: χ^2 = 12.4; p = 0.002) the risk of progression was a high NLR2 value (HR = 2.2429; 95% CI 1.2881–3.9052) and the factor significantly decreasing the risk of death was non-SqCC diagnosis (HR = 0.5203; 95% CI 0.2978–0.909).

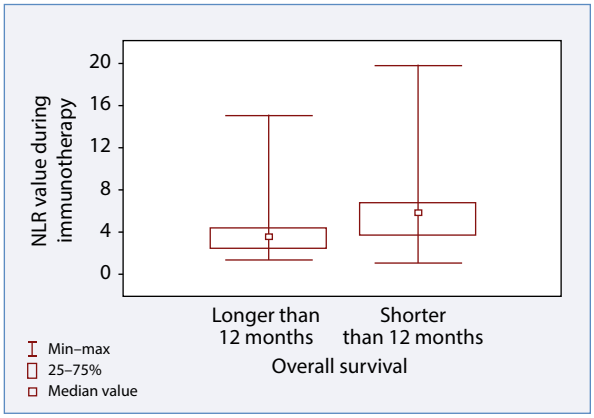

Figure 5. Neutrophil-to-lymphocyte ratio (NLR) 2 values in non-small cell lung cancer (NSCLC) patients with short and long overall survival (mNLR2 = 3.66 *vs.* 5.87; p = 0.00294)

Discussion

The use of neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios in monitoring the effectiveness of immunotherapy in cancer patients highlights their potential as non-invasive and easily available biomarkers for assessing treatment response and guiding clinical decisions [6]. Several studies have demonstrated the prognostic significance of the NLR and PLR in various cancers, including lung cancer, where immunotherapy has emerged as a promising treatment modality [6, 7]. Let us consider the validity of measuring these parameters in cancer patients treated with immunotherapy.

Firstly, the NLR and PLR reflect the interaction between inflammatory reaction and tumor cells within the tumor microenvironment (TME) [6, 9]. A high number of neutrophils and platelets, along with a low number of lymphocytes, indicate systemic inflammation and immunosuppression, which are associated with poorer treatment outcomes [6, 9]. Conversely, low NLR and PLR values suggest a more favorable immune response, potentially leading to a better response to immunotherapy. In our study, the median value of the NLR examined at initiation of immunotherapy as well as at first clinical control of its efficacy was significantly lower in patients with controlled disease than in patients with disease progression. We did not observe such changes for the remaining examined parameters, i.e. the PLR, delta PLR, or delta NLR. Elevated levels of neutrophils often signify an inflammatory response, which is common in cancer patients due to tumor-related inflammation or treatment-related side effects. Generally, immunotherapy is intended to stimulate the patient's

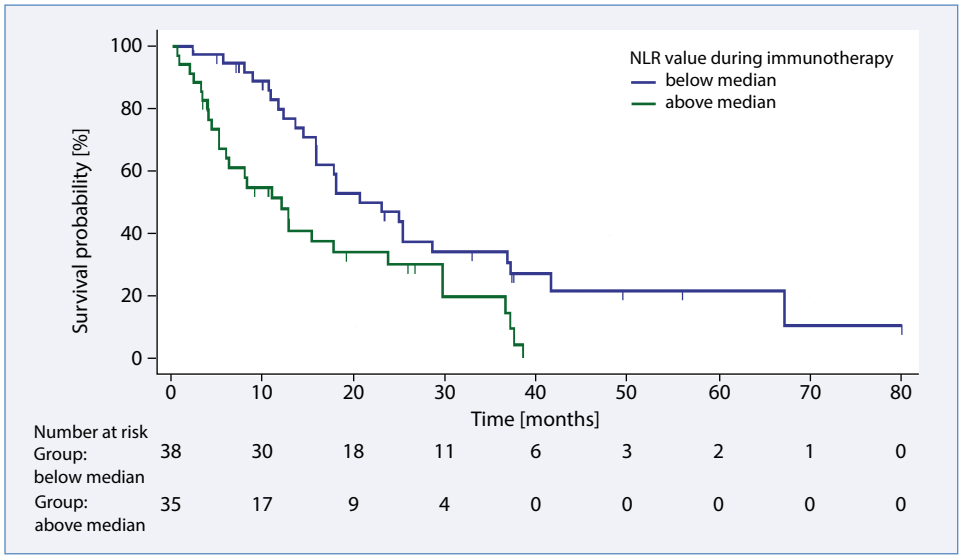

Figure 6. Risk of death in non-small cell lung cancer (NSCLC) patients with neutrophil-to-lymphocyte ratio (NLR) 2 value below and above the median [hazard ratio (HR) = 2.2759; 95% confidence interval (CI) 1.2805–4.0451; p = 0.0051]

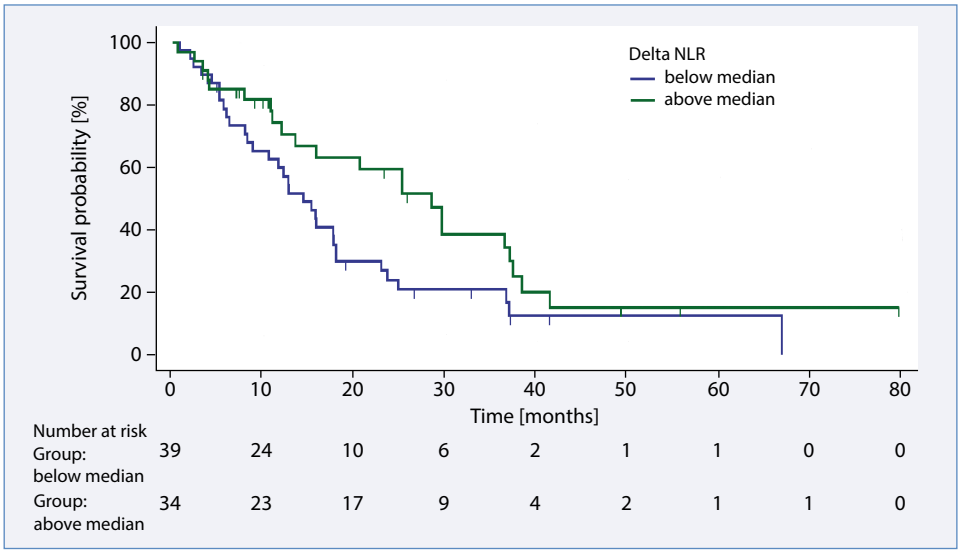

Figure 7. Risk of death in non-small cell lung cancer (NSCLC) patients without reduction in neutrophil-to-lymphocyte ratio (NLR) during immunotherapy and with a high reduction in NLR [hazard ratio (HR) = 1.7699; 95% confidence interval (CI) 1.0254–3.0551; p = 0.0404]

immune system, and the main cells' subpopulation responsible for its' cytotoxicity are T lymphocytes. The possible reason for only the NLR2 being the most significant may be that immunotherapy has influenced this indicator through recruitment of T lymphocytes to the tumor site so this effect may be observed after treatment begins. If the differences between values before treatment were not significant, then the delta values would not be statistically significant either.

Platelets have immunomodulatory functions and can interact with immune cells to suppress anti-tumor immune responses. High PLR levels may be associated with immune suppression and impaired lymphocyte function, limiting the ability of the immune system to recognize and eliminate cancer cells, thus reducing the efficacy of immunotherapy. As for the PLR, the elevation of platelet count accelerates tumor progression by promoting the formation of new blood vessels and the production of adhesion molecules [10]. The platelet count is a non-specific indicator of the tumor, and it increases in patients with advanced-stage cancer, so the PLR1 may not differ significantly between groups of patients with favorable and non-favorable immunotherapy outcomes. Moreover, PLR fluctuations are small, due to the large numerical differences between platelet counts and lymphocyte counts because for the fluctuations to occur, there would have to be large changes in platelet counts. Additionally, the group may not have been numerous enough to show significant differences.

In our opinion, the PLR is less specific to immunotherapy outcomes, on the other hand, it may serve as a prognostic marker for identifying patients with more aggressive disease who are less likely to benefit from immunotherapy. It is important to note that compared to the NLR, the relationship between the PLR and immunotherapy efficacy is less well-established and supported by fewer studies. While some research suggests a potential association between a high PLR and reduced response to immunotherapy, we did not observe this correlation in our study. Further investigation is needed to validate these findings and elucidate the underlying mechanisms.

Analysis of parameters for assessing treatment effectiveness that are easily available to clinicians is increasingly described in the literature. Liu et al. [11] analyzed whether hematological parameters such as systemic immune-inflammation index (SII), NLR, or PLR could be related to the effectiveness of nivolumab used in second or subsequent lines of treatment in NSCLC patients. The SII is a relatively new marker of inflammation that combines neutrophil, platelet, and lymphocyte counts. Liu et al. [11] showed that patients with a low baseline SII index (measured at the time of treatment introduction) achieved significantly longer progression-free survival and overall survival compared to patients with a high SII index. Moreover, single analysis of the NLR indicated that a low NLR before treatment was significantly correlated with longer OS and PFS compared to the group of patients with a high NLR (median OS 19.8 months *vs*. 8.9 months; median PFS 6.7 months *vs*. 3.9 months) [11]. The results of our study are similar; a low NLR1 and NLR2 were associated with significantly longer PFS.

Considering first-line immunotherapy, another very interesting issue is whether the NLR could be associated with clinical outcomes for NSCLC patients with high PD-L1 expression. Alessi et al. [12] examined a total of 221 patients treated with first-line pembrolizumab and determined the optimal NLR cut-off to differentiate treatment responders from non-responders (cut-off at 2.6 NLR ratio). Significantly higher overall response rates, median progression-free survival, and median overall survival were observed in patients with a low NLR (< 2.6) compared with patients with a high NLR median value (≥ 2.6). After adjusting for clinical parameters (e.g. age, sex, tobacco use, performance status, histology, serum albumin level, oncogenic driver status, and PD-L1 expression), a low NLR was confirmed to be an independent predictor of longer PFS and OS [12]. Our results, however, performed in the group of NSCLC patients treated in second line, appear to agree with those published in the literature. In our study, the risk of progression did not depend on the age, sex, pathological diagnosis, cigarette smoking status, type of immunotherapy, percentage of tumor cells with PD-L1 expression, nor NLR1, PLR1, PLR2, delta NLR, or delta PLR values. In our patients, the only factor that significantly increased the risk of progression was a high NLR value at the first follow-up (median value of NLR2 ≥ 3.67).

Moreover, the independent effect of the NLR on overall survival in patients with NSCLC as well as other tumors (renal cell carcinoma and melanoma) was observed in a sub-analysis of the INVIDIa-2 study [10]. Anpalakhan et al. [10] showed significantly longer OS in patients with low NLR values (< 3.4). They concluded that the NLR could significantly predict OS in the first line as well as in second and subsequent lines of treatment and could be defined as a prognostic factor in NSCLC, renal cell carcinoma, and melanoma patients treated with ICIs [10]. In our study, patients with overall survival longer than 1 year had a significantly lower median NLR2 than patients with OS shorter than 1 year. Moreover, the factor that significantly increased the risk of death in our group was a high NLR2 value.

Secondly, dynamic changes in the NLR and PLR during the course of treatment can serve as indicators of treatment response or disease progression [13, 14]. Studies have shown that decreases in the NLR and PLR following immunotherapy initiation are associated with improved overall survival and progression-free survival in cancer patients [6, 13, 14]. Conversely, sustained or increased NLR and PLR levels may indicate treatment resistance or disease progression, prompting alternative therapeutic strategies [6, 13, 14]. In our patients, a reduction in the NLR value during immunotherapy did not decrease the risk of progression significantly. However, patients who did not have a reduction in the NLR during immunotherapy (delta NLR below the median, low NLR2 value) had a significantly higher risk of death than other patients. Hwang et al. [9] observed that an increase in the NLR after two cycles of immunotherapy was associated with significant shortening of progression-free survival in NSCLC patients. Similar results were presented by Kuzman et al. [15] and Bagley et al. [8]. In both studies, a reduction in the NLR 6 ± 2 weeks after ICI initiation compared to baseline levels was significantly associated with improved outcomes in patients with renal cell carcinoma and with NSCLC [8, 15]. Therefore, it seems that a decrease in the NLR value during immunotherapy is an indicator of the effectiveness of this treatment method. An increase in the number of lymphocytes induced by immunotherapy is observed. This would prove that ICIs do not only activate lymphocytes by blocking the PD-1 — PD-L1 pathway but also increase the number of peripheral lymphocytes, which additionally intensifies the anti-tumor immune response. During effective immunotherapy, the specific immune response increases, but the non-specific inflammatory response decreases. However, in patients not responding to immunotherapy, this effect is not observed.

Moreover, incorporation of the NLR and PLR into existing prognostic models or scoring systems may enhance their predictive accuracy for immunotherapy response [6, 8, 9]. By combining these factors with other clinical and molecular biomarkers, such as PD-L1 expression or tumor mutational burden (TMB), clinicians can better stratify patients into risk groups and tailor treatment approaches accordingly [5, 6, 8]. However, it is essential to acknowledge the limitations and variability associated with NLR and PLR measurements, including differences in cut-off values, inconsistencies in laboratory assays, and potential confounding factors such as concomitant medications or comorbidities. Additionally, while the NLR and PLR hold promise as adjunctive biomarkers for monitoring immunotherapy effectiveness, they should be interpreted within the context of comprehensive clinical assessment and imaging studies to make informed treatment decisions.

Conclusions

In conclusion, the NLR and PLR represent promising biomarkers for monitoring immunotherapy effectiveness in cancer patients, offering insights into the dynamic interplay between the host immune system and tumor biology. Further research is warranted to validate their utility in larger patient cohorts and standardize their incorporation into clinical practice guidelines.

Article Information and Declarations

Data availability statement

Original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

Ethics

The research was approved by the bioethics committee at the Medical University of Lublin (KE-0254/95/2018). Informed consent was obtained from all patients.

Author contributions

T.J.: article concept, writing, clinical data collection, literature data collection; N.K., A.G.: writing, clinical data collection, literature data collection; K.W.-K.: writing, supervising the article; P.K.: statistical analysis, revising the article; I.C., M.S.: clinical data collection; J.M.: revising the article.

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Conflict of interest

The authors declare no conflict of interest.

Supplementary material

None.

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