Original Article

Prognostic significance of neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in second-line immunotherapy for patients with non-small cell lung cancer

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Background: Immune checkpoint inhibitors remain a therapeutic option for chemotherapy pretreated patients with advanced non-small cell lung cancer (NSCLC). Given the lack of biomarkers, there is a need to look for predictive factors in this population. Inflammatory markers derived from peripheral blood cells (PBCs) may be a valuable diagnostic tool to assess the likelihood of clinical benefit. The aim of the study was to evaluate the efficacy of the treatment and to analyse the NLR and PLR predictive values

Methods: Patients eligible for nivolumab or atezolizumab treatment in routine practice in two cancer centres between 2018 and 2021 were retrospectively analysed. Good performance status (ECOG 0–1), absence of *EGFR*, *ALK*, *ROS1* alterations and no previous immune checkpoint inhibitors treatment were the inclusion criteria. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were calculated based on the results obtained before the start of immunotherapy. The median value was used as the cut-off point for comparative analyses.

Results: The group of 332 patients was enrolled, 73.5% patients were in stage IV. The median NLR in the study group was 3.86±4.9 and the median PLR was 193.24±172.87. In the entire study group the disease control rate was 59 %, median PFS was 3.3 months [95% confidence interval (CI): 3.77 to 4.4], while median OS 11.57 months (95% CI: 9.03 to 12.73). In a univariate analysis the baseline values of NLR and PLR had a significant impact on survival, while age, gender, programmed death ligand 1 (PD-L1) expression, or type of treatment were not significant. In the multivariate Cox logistic regression model, a high value of NLR was the only factor that increased the risk of death [hazard ratio (HR) =1.6315, 95% CI: 1.2836 to 2.0737, P<0.001].

Conclusions: Inflammatory indices derived from peripheral blood cells—NLR and PLR—can help assess the prognosis of patients receiving immunotherapy. They also appear to be independent prognostic factors with regard to for PFS and OS.

Keywords: Neutrophil-to-lymphocyte ratio (NLR); platelet-to-lymphocyte ratio (PLR); immunotherapy; non-small cell lung cancer (NSCLC)

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Introduction

Background

Immune checkpoint inhibitors are the standard of treatment for patients diagnosed with advanced non-small cell lung cancer (NSCLC). Nivolumab, atezolizumab and pembrolizumab remain the treatment of choice for patients who receive platinum-based chemotherapy alone in the first-line setting. The available data suggest that immunotherapy in second-line treatment achieves a 5-year survival rate of approximately 18% (1,2).

At the same time, a subset of patients experience rapid disease progression and death in the first few weeks of follow-up, despite a good performance status at the time of entry into treatment (3). Therefore, it is important to look for additional factors that could better indicate optimal patients for the immunotherapy. This is particularly important in patients qualified for second-line immunotherapy. Patients may be qualified for nivolumab or atezolizumab therapy regardless of programmed death ligand 1 (PD-L1) expression. This indicates a lack of predictive factors for immunotherapy in this group of patients.

Indexes based on blood morphology parameters could provide a simple diagnostic tool. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are considered parameters associated with systemic inflammation, with potentially negative prognostic significance. High levels of these indices correlate with greater disease severity (4). It is important to determine the predictive value of these indices for the effectiveness of immunotherapy, particularly in patients treated in clinical practice. In this article, we present an analysis of a large group of patients treated with nivolumab and atezolizumab.

Objectives

The aim of the study was to evaluate the efficacy of the treatment and to analyse the NLR and PLR values, with particular attention to the profile of patients with the highest risk of early progression and death. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-675/rc).

Highlight box

Key findings

- Our study demonstrated that immune checkpoint inhibitors are a valuable therapeutic option for advanced non-small cell lung cancer (NSCLC) patients after the failure of chemotherapy in clinical practice. Given the lack of biomarkers, there is a need to look for predictive factors in this population. Inflammatory markers derived from peripheral blood cells (PBCs) may be a valuable diagnostic tool to assess the likelihood of clinical benefit.

What is known and what is new?

- Several inflammatory indices based on PBC, including neutrophil-tolymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), have been tested for pretreated NSCLC patients qualified to immunotherapy. Higher value indices were related to poor outcomes, and the majority of data were related to NLR which is a surrogate for tumour inflammation.
- Our study determined the association between the baseline PLR and NLR and the treatment response, progression-free survival and overall survival. Platelets are involved in processes related to tumour promotion, and PLR seems to be important variable. Our study have shown that high NLR (>3.86) value is independent negative prognostic factor for immune checkpoint inhibitors.

What is the implication, and what should change now?

- There is still unmet need to investigate predictive and prognostic biomarkers of immune checkpoint inhibitors in pretreated patients. Inflammatory indices based on PBC are simple, reproducible and inexpensive tools to help identify patients who are less likely to benefit from monotherapy with immune checkpoint inhibitors. It is worthy to use them in clinical practice.

Methods

Inclusion criteria

All subsequent patients qualified for the treatment with nivolumab (240 mg i.v. every 14 days) or atezolizumab (1,200 mg i.v. every 21 days) as part of clinical practice between 2018 and 2021 were retrospectively analysed. Eligibility criteria included diagnosis of stage III or IV NSCLC, a previous line of chemotherapy, good performance status [Eastern Cooperative Oncology Group (ECOG) 0–1], measurable lesions detectable by computed tomography (CT), absence of clinically significant autoimmune disease or molecular abnormalities of the *EGFR* (epidermal growth factor receptor) and *ALK* (anaplastic lymphoma kinase) genes. Patients with brain metastases were eligible as long as they had received local treatment and were on a stable dose of corticosteroids within four weeks before starting immunotherapy. Previous use of PD-1/PD-L1 inhibitors was not allowed. The patients were assigned nivolumab or atezolizumab at the discretion of the physician. Clinical and pathological data

were obtained from available electronic medical records. The date of death was obtained from the National Cancer Registry. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The research was approved by the Bioethics Committee of the Medical University of Lublin (No. KE-0254/95/2018). Informed consent was obtained from all patients.

Monitoring effectiveness

A contrast-enhanced CT scan was performed before starting immunotherapy. The response to the treatment was evaluated using CT scans performed every 3 months or more frequently if the progression of the disease was clinically suspected. Response to the treatment was evaluated according to the Response Evaluation Criteria for Solid Tumours (RECIST 1.1). The treatment was continued until documented objective progression of the disease, unacceptable toxicity, or death for other reasons. Overall survival was defined as the time from the initiation of second-line immunotherapy to death. Progression-free survival was defined as the time from the initiation of the immunotherapy to progression according to RECIST 1.1, clinical progression or death, whichever occurred first. Patients alive and without progression at the last observation were censored.

Calculation of the NLR and PLR

The value of NLR was calculated by dividing the number of neutrophils by the number of lymphocytes in standard peripheral blood count analysis. The PLR was calculated by dividing the number of platelets by the number of lymphocytes obtained from the same blood sample. The NLR and PLR values were calculated when NSCLC patients were qualified for the second line of immunotherapy.

Statistical analysis

Kaplan-Meier survival and multiparameter Cox regression analysis were used to calculate the risk of progression or death in different groups of patients. The Mann-Whitney *U* test was used to assess differences in progression-free survival and overall survival depending on demographic factors, type of treatment, and NLR and PLR values. Results are presented as medians and maximum and minimum values (min-max). A P value below 0.05 was considered statistically significant. Statistical analysis was performed using Statistica 13.3 (TIBCO Software Inc, Palo Alto, USA) and MedCalc (MedCalc Software Ltd., Ostend, Belgium) software.

Results

Characteristics of the patients

The group of 332 patients was enrolled, of which 172 (51.8%) patients received atezolizumab and 160 (48.2%) patients received nivolumab in second-line immunotherapy. There were 145 (43.7%) women and 187 (56.3%) men. The median age of the patients was 67±7.5 years. Of 332 patients, 244 (73.5%) patients were in stage IV and 88 (26.5%) patients were in stage IIIB according to the eighth classification of TNM (tumour, node metastasis) classification. There were 125 (37.7%) patients diagnosed with squamous cell carcinoma and 207 (62.3%) patients with non-squamous cell carcinoma. The PD-L1 expression (SP263 Ventana) was evaluated in 135 (40.7%) patients. Among them, any expression of PD-L1 expression [over 1% of tumour cells (TC) expressing PD-L1] was found in 71 (52.6%) patients and no expression of PD-L1 was found in 64 (47.4%) patients. The median percentage of TC with expression of PD-L1 was 2%±23.4%.

Most of the patients were treated with cisplatin and pemetrexed and cisplatin and vinorelbine in the first line setting.

At the end of follow-up (November 2023), 82% of the patients died, 18.1% remained alive, among them, 9% of the patients were still receiving immunotherapy. The median NLR in the study group was 3.86±4.9 and the median PLR was 193.24±172.87. Detailed demographic and clinical characteristics of the entire study group are presented in *Table 1*.

Response to treatment

In the entire study group, partial response (PR) was observed in 87 (26.2%) patients, disease stabilisation (SD) in 109 (32.8%) patients, and disease progression (PD) in 136 (41%) patients. Progression occurred slightly more frequently (44.2% *vs.* 36.9% of patients, P=0.18, χ^2=1.836) and remission occurred slightly less frequently (22.7% *vs.* 30.6% of patients, P=0.10, χ^2=2.69) in patients receiving atezolizumab compared to patients treated with nivolumab. SD occurred in both groups with similar frequency (33.1%

Table 1 Characteristics of the study population (N=332)

Characteristics	N (%)
Age	
<67 years	112 (33.7)
≥67 years	220 (66.3)
Gender	
Male	187 (56.3)
Female	145 (43.7)
Smoking status	
Smokers	254 (76.5)
Non-smokers	36 (10.8)
Unknown	42 (12.7)
Histopathology	
SqC	125 (37.7)
AdC	181 (54.5)
NSCLC NOS	20 (6.0)
LCC	5 (1.5)
Ad-Sqc	1 (0.3)
Clinical stage	
IIIB	88 (26.5)
IV	244 (73.5)
PD-L1 IHC	
<1%	64 (47.4)
≥1%	71 (52.6)
Second-line immunotherapy	
Atezolizumab	172 (52.8)
Nivolumab	160 (48.2)
First-line therapy	
Cisplatin/pemetrexed	95 (28.8)
Cisplatin/vinorelbine	88 (26.7)
Carboplatin/pemetrexed	67 (20.4)
Carboplatin/vinorelbine	55 (16.7)
Monotherapy (gemcitabine, vinorelbine)	24 (7.4)
NLR median	3.86
PLR median	193.24

AdC, adenocarcinoma; CI, confidence interval; HR, hazard ratio; IHC, immunohistochemistry; LCC, large cell carcinoma; NSCLC, non-small cell lung cancer; NOS, not otherwise specified; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival; PLR, platelet-to-lymphocyte ratio; SqC, squamous carcinoma.

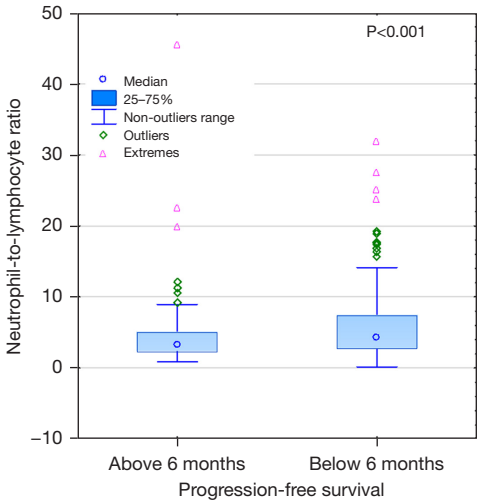

Figure 1 NLR value in patients with progression-free survival shorter than and longer than 6 months. NLR, neutrophil-to-lymphocyte ratio.

vs. 32.5% of the patients). These differences were not statistically significant.

Response to treatment in relation to NLR/PLR

Patients who achieved SD had significantly lower values of NLR and PLR compared to patients with PR and PD (P<0.001 and P=0.003 for NLR and PLR in the SD group compared to the PR group, as well as P=0.003 and P=0.01 for NLR and PLR in the SD group compared to the PD group). However, the values of NLR and PLR in patients with PR and PD as well as patients with disease control and PD were not significantly different.

Progression-free survival

In the general population, the median PFS was 3.3 months (95% CI: 3.77 to 4.4), in 21.4% of the patients PFS exceeded 12 months.

Progression-free survival in relation to NLR/PLR

We performed analyses of differences in NLR and PLR values in patients with PFS below and above 6 months. Patients with PFS shorter than 6 months had significantly higher NLR than patients with PFS longer than 6 months (P<0.001, *Figure 1*). We did not obtain statistically significant differences in PLR value in patients with short and long PFS (below and above 6 months) (*Figure 1*). Differences in PLR in these two groups of patients were

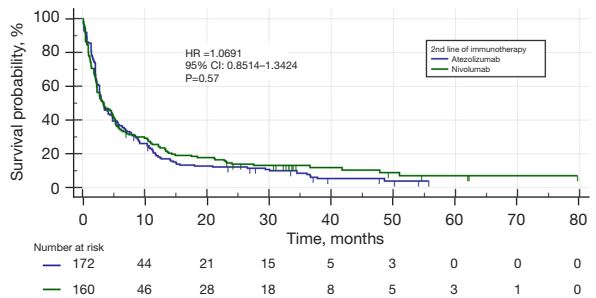

Figure 2 Kaplan-Meier curves that illustrate the probability of progression-free survival in patients treated with atezolizumab and nivolumab. CI, confidence interval; HR, hazard ratio.

not statistically significant. The risk of progression did not depend on age, gender, type of cancer, stage of the disease, PD-L1 expression, or type of the second-line immunotherapy (*Figure 2*, *Table 2*). The risk of progression was significantly lower in patients with NLR and PLR values below the median compared to patients with values above the median (*Figures 3*,*4*, *Table 2*). In the multivariate Cox logistic regression model, a high value of NLR was the only factor that increased the risk of progression (HR =1.6552, 95% CI: 1.3185 to 2.0781, P<0.001) in patients receiving second-line immunotherapy (overall model fit: χ^2=18.751, P<0.001).

Overall survival

The median overall survival calculated from the beginning of immunotherapy was 11.57 months (95% CI: 9.03 to 12.73). In the entire population, 53.6% of the patients survived at least 12 months.

Overall survival in relation to NLR/PLR

Patients with a survival longer than 12 months had significantly lower NLR and PLR values compared to patients with a shorter survival time (*Figures 5*,*6*). There was no correlation between the risk of death and age, sex, histopathological diagnosis, stage of the disease, or type of immunotherapy (*Figure 7*, *Table 1*). The risk of death was significantly lower in patients with low NLR and PLR values compared to patients with NLR and PLR values above the median (*Figures 8*,*9*, *Table 1*). In the multivariate Cox logistic regression model, a high value of NLR was the only factor that increased the risk of death (HR =1.6315, 95% CI: 1.2836 to 2.0737, P<0.001) in patients receiving second-line immunotherapy (overall model fit: χ^2=15.992, P<0.001).

In summary, in the entire population, the baseline value of NLR and PLR had a significant impact on survival, while age, sex, or type of treatment were not significant. The univariate analysis for PFS and OS with respect to clinical and laboratory factors is summarised in *Table 2*.

Discussion

It is widely accepted that inflammation plays a crucial role in tumour progression and can affect survival in patients with different types of cancer. Previous data have shown that elevated baseline levels of NLR and PLR are associated with a poor prognosis in the general population of patients with NSCLC (4,5). The purpose of the present study was to evaluate the prognostic value of these parameters in the group of 332 patients who received immune checkpoint inhibitors in the second-line treatment of advanced NSCLC. The median baseline (assessed at the time of the patient's initiation of immunotherapy) for the entire group of patients was 3.86 for the NLR index and 193 for the PLR index.

To the best of our knowledge, the data we presented here represent the largest population of patients treated with nivolumab and atezolizumab that has been analysed to date in the context of the predictive value of baseline NLR and PLR (6-10). Russo *et al.* compared baseline peripheral blood count parameters in 62 patients receiving nivolumab or docetaxel. Baseline neutrophilia (defined as ≥7,500 cells/μL) and thrombocytosis (defined as ≥450×10^3/μL) were associated with a significant reduction in response probability both in the global study population (P=0.0003 and P=0.002, respectively) and in the nivolumab (P=0.0001 and P=0.0004, respectively) and docetaxel (P=0.0006 and P=0.0042, respectively) subgroups. The authors defined a high NLR of ≥3 and a high PLR of ≥160. A high NLR was associated with a lack of response in patients receiving nivolumab, but no such association was observed in the docetaxel arm. Patients with high PLR were also observed to not benefit significantly from treatment in the entire study group compared to patients with low PLR (median OS 4.0 *vs.* 12.0 months; P=0.003) (11). However, when analysing the effectiveness of immunotherapy or chemotherapy separately, a high PLR was not significantly associated with a lack of benefit, regardless of the treatment used. In our study, we did not use a chemotherapy-treated control group, although the study cited above and other reports suggest that the value of NLR is important in patients treated with immunotherapy

Table 2 Univariate analysis for PFS and OS

Characteristics	N (%)	PFS (months)			OS (months)		
		Median	HR (95% CI)	P	Median	HR (95% CI)	P
Age				0.55			0.17
<67 years	112 (33.7)	2.97	0.9301 (0.7331–1.18)		11.8	0.8410 (0.6565–1.0774)	
≥67 years	220 (66.3)	3.43			10.8		
Gender				0.07			0.09
Male	187 (56.3)	3.43	1.2397 (0.9857–1.5591)		10.77	1.2323 (0.97–1.5656)	
Female	145 (43.7)	3.3			11.73		
Histology				0.66			0.70
Non-SqC	207 (62.3)	2.97	1.0535 (0.8348–1.3296)		10.47	1.0484 (0.8223–1.3391)	
SqC	125 (37.7)	3.5			12.17		
Clinical stage				0.22			0.75
IIIB	88 (26.5)	2.77	1.1793 (0.9063–1.5345)		12.7	1.0454 (0.7967–1.3716)	
IV	244 (73.5)	3.47			11.3		
PD-L1 IHC				0.39			0.20
<1%	64 (47.4)	2.73	1.1728 (0.8177–1.6821)		10.57	1.2807 (0.8783–1.8673)	
≥1%	71 (52.6)	4.73			13.43		
Second-line immunotherapy				0.57			0.39
Atezolizumab	172 (52.8)	3.43	1.0691 (0.8514–1.3424)		10.9	1.1093 (0.8736–1.4085)	
Nivolumab	160 (48.2)	3.3			12.17		
NLR				<0.001			<0.001
< median	166 (50)	4.93	0.5901 (0.4669–0.7459)		14.3	0.6047 (0.4738–0.7717)	
≥ median	166 (50)	2.13			8.17		
PLR				0.03			0.003
< median	166 (50)	4.7	0.7769 (0.6183–0.9763)		14.33	0.6958 (0.5466–0.8857)	
≥ median	166 (50)	2.73			8.9		

AdC, adenocarcinoma; CI, confidence interval; HR, hazard ratio; IHC, immunohistochemistry; LCC, large cell carcinoma; NSCLC, non-small cell lung cancer; NOS, not otherwise specified; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival; PLR, platelet-to-lymphocyte ratio; SqC, squamous carcinoma.

rather than chemotherapy (11,12). The meta-analysis by Liu *et al.* summarised the studies including data from 34 real-world trials involving more than 3,120 patients. The authors found that high levels of NLR and PLR at baseline were significantly associated with shorter overall survival and progression-free survival. However, they also observed that a low lymphocyte/monocyte ratio (LMR) was associated with a worse prognosis for patients (13). Liu *et al.* did not provide an analysis of other clinical and laboratory factors in their article and also noted that the different cutoff points in the trials included in the analysis made it difficult to draw firm conclusions. Most of the authors did not analyse individual blood count parameters, only the NLR index. In our study, both NLR and PLR were significantly lower in patients with longer survival. We found NLR <3.86 to be independent significant favourable prognostic factors. The study by Liu *et al.* showed similar data—many of the clinical characteristics studied, such as patient age, sex, smoking history, patient

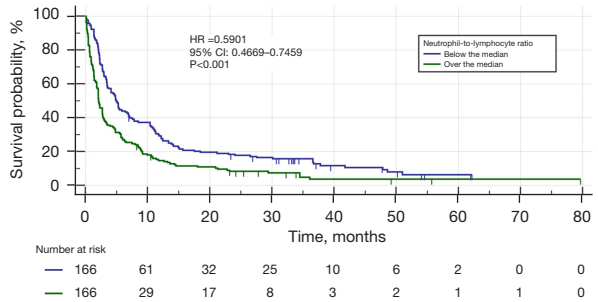

Figure 3 Kaplan-Meier curves showing the probability of progression-free survival in patients receiving second-line immunotherapy depending on the NLR value. CI, confidence interval; HR, hazard ratio; NLR, neutrophil-to-lymphocyte ratio.

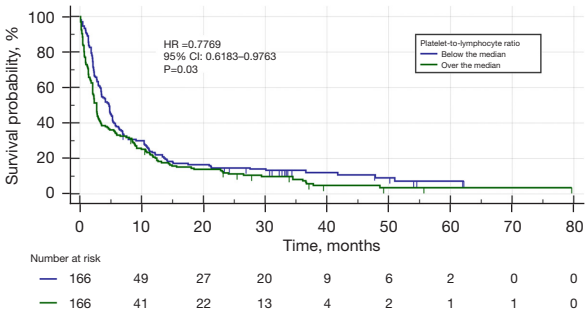

Figure 4 Kaplan-Meier curves showing the probability of progression-free survival in patients receiving second-line immunotherapy depending on the PLR value. CI, confidence interval; HR, hazard ratio; PLR, platelet-to-lymphocyte ratio.

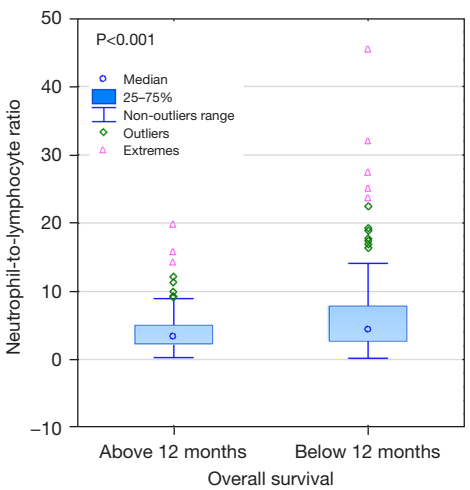

Figure 5 NLR value in patients with overall survival shorter and longer than 12 months. NLR, neutrophil-to-lymphocyte ratio.

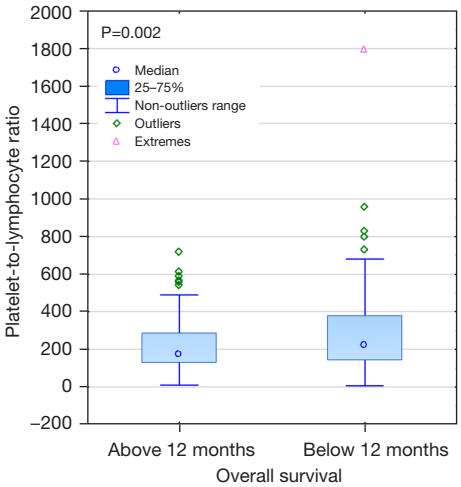

Figure 6 Value of PLR in patients with overall survival less than and for more than 12 months. PLR, platelet-to-lymphocyte ratios.

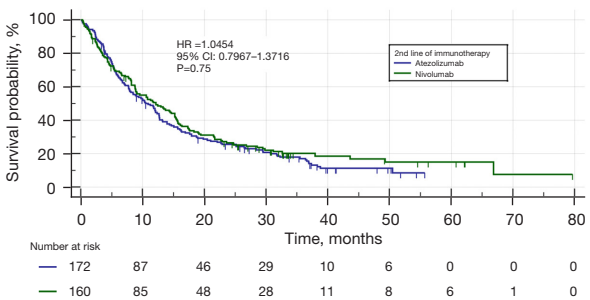

Figure 7 Kaplan-Meier curves that illustrate survival probability in patients treated with atezolizumab and nivolumab. CI, confidence interval; HR, hazard ratio.

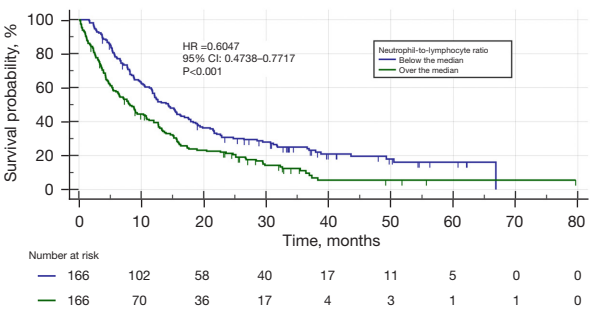

Figure 8 Kaplan-Meier curves that illustrate survival probability in patients who received second-line immunotherapy with a high and low value of NLR. CI, confidence interval; HR, hazard ratio; NLR, neutrophil-to-lymphocyte ratio.

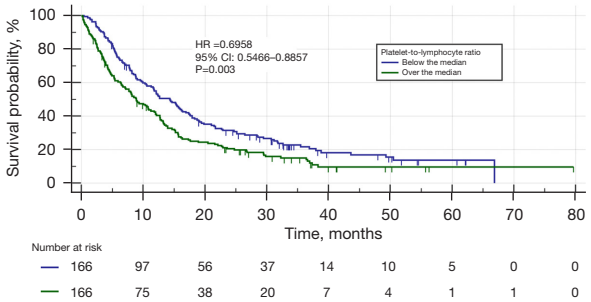

Figure 9 Kaplan-Meier curves that illustrate survival probability in patients receiving second-line immunotherapy with high and low PLR values. CI, confidence interval; HR, hazard ratio; PLR, platelet-to-lymphocyte ratio.

stage and histopathological diagnosis, did not have a significant impact on the risk of disease progression, while laboratory parameters such as low NLR, low PLR, and low systemic immune inflammation index (SII) had a significant impact in multivariate analysis (14).

It is intriguing that differences in NLR and PLR values were observed between patients with disease stabilization and disease progression, but not between patients with disease remission and disease progression.

This may be explained by the fact that patients with disease remission represent a highly heterogeneous group. In some of them, despite the initial benefit of immunotherapy, progression occurs within 6 months of observation. Patients with disease stabilization constitute a more homogeneous group. Stabilization lasts longer. This may be due to the mechanisms of the immunotherapy. The treatment works slowly, leading to the dominance of the immune system over the ongoing neoplastic process. However, initial remission may trigger mechanisms that tip the balance in tumour escape from immune surveillance. Therefore, the tumour rapidly learns to inactivate the immune system in the case of tumour remission, which is not observed in the case of stabilized tumour disease.

It is legitimate to ask what NLR and PLR actually are and what variables affect its value. The prognostic value of NLR in immunotherapy-treated cancer patients could be explained by the different functions of the two cell populations that make up this index in the body (15). Stimulated by inflammation, neutrophils can secrete large amounts of pro-inflammatory cytokines such as interleukin 1 (IL-1), IL-6, and tumour necrosis factor alpha (TNF-α), migrate to the site of tumour formation and create a favourable microenvironment for tumour development and progression (16). An increase in NLR means an increase in neutrophils and a decrease in lymphocytes, but also—for example—a decrease in the number of lymphocytes with stable neutrophil levels. It should be noted that neutrophils may have dual functions in relation to the tumour. Tumour-associated neutrophils (TAN) can promote tumourigenesis by driving angiogenesis, remodelling the extracellular matrix, and creating an immunosuppressive environment; they suppress T-lymphocyte activation (17). Neutrophils also maintain tumour proliferation by producing epidermal growth factor (EGF), hepatocyte growth factor (HGF), and platelet-derived growth factor (PDGF) (17). Therefore, higher levels of NLR may reflect the promotion of pro-tumour activity, favouring tumour progression, which is defined as an adverse prognostic factor. At the same time, neutrophils can mediate the antitumour response and are involved in different mechanisms of antitumour resistance, including direct cytotoxic activity against tumour cells, the activation of T-cell-dependent antitumour immunity or antimicrobial activity. Cytokines present in the tumour microenvironment—granulocyte-macrophage colony stimulating factor (GM-CSF) and interferon-γ (IFNγ)—promote the maturation of immature neutrophils into antigen-presenting cells (APC) that express class I and class II molecules of the major histocompatibility complex (MHC) and the co-stimulatory molecules CD86, 4-1BB ligand (4-1BBL) and OX40 ligand (OX40L) (17). However, with cancer progression, neutrophils appear to undergo a functional switch to an immunosuppressive, pro-cancer state (17).

The total number of lymphocytes in peripheral blood indicates the pool of circulating cells without subtype specification. Lymphocytes also differ in their potential anticancer activity (18). Cytotoxic T lymphocytes (CTLs), defined by the expression of the CD8 glycoprotein on their surface, recognise antigens presented by MHC class I molecules and receive a signal for activation from CD4 positive helper lymphocytes (mainly through their secreted IL-2) and from antigen-presenting cells in the lymph node. CTLs are responsible for the destruction of tumour cells through a mechanism of cytotoxicity. Helper T cells (Th), defined by the expression of the CD4 glycoprotein on their surface, are responsible for promoting humoral and cell responses through direct receptor contact with other cells and the secretion of specific cytokines. This group includes Th1 helper lymphocytes, that secrete cytokines, IFN-g (gamma interferon), IL-2, TNF-a and activate macrophages and CTLs; they are responsible for the development

of cellular immune responses, including antimicrobial and anticancer responses; and Th2 helper lymphocytes, which secrete the cytokines IL-4, IL-5, and IL-13 and activate eosinophils, basophils, and B lymphocytes; they are responsible for the development of humoral responses. Regulatory T lymphocytes, which secrete IL-10 and IL-25 and are responsible for inhibiting excessive anti-inflammatory and hypersensitivity responses. Regulatory T lymphocytes protect the body against autoimmunity, but their activity may contribute to the suppression of the immune response in cancer (18).

Low levels of circulating lymphocytes may result from the high infiltration of the tumour microenvironment by these cells. However, paradoxically, in combination with the activity of other cells of myeloid origin present there and the activity of highly immunosuppressive substances produced by tumours (e.g., IL-10, TGF-β), a decrease in the percentage of lymphocytes in peripheral blood in favour of their presence in tumour tissue does not always translate into efficacy of immunotherapy. As tumour cells develop mechanisms to escape the immune system, lymphocytes are depleted. Prolonged stimulation of the immune system induces defence mechanisms to silence its activity, including the induction or increased expression of receptors responsible for suppressing the immune response. A major role in this mechanism is played by regulatory T lymphocytes, dendritic cells, and tumour cells themselves (interaction between the best known molecules with immunosuppressive properties, namely PD-L1 and PD-1 and B7-1 or B7-2 and CTLA-4). Thus, despite the accumulation of lymphocytes in the microenvironment, they become nonfunctional. This may explain the loss of clinical benefit of immunotherapy, which is correlated with an increase in NLR levels (19).

In our study, we analyse the predictive value of both baseline NLR and PLR in a specific population of patients eligible for second-line immunotherapy. PLR seems to be a less appreciated parameter, but the role of platelets in processes related to tumour promotion is important. Data from the general population of immunotherapy-treated patients included small groups of patients, and pooled analyses of these observations have previously been published (20,21).

The role of platelets in the modelling of the response to immune checkpoint inhibitors is not fully understood. However, it should be noted that platelet-derived nucleotides can promote transendothelial migration and metastasis of tumour cells through the P2Y2 receptor (purinergic receptor 2) (22). Furthermore, platelets secrete platelet-derived growth factor (PDGF), platelet activating factor (PAF), and vascular endothelial growth factor (VEGF) to promote angiogenesis and tumour growth (22). Platelets have been postulated to interact with lung cancer cells and the PD-L1 protein. The PD-L1 protein can be translocated from NSCLC cells to platelets through fibronectin 1, integrin α5β1 and in a glycoprotein Ibα-dependent manner, and that platelets expressing PD-L1 can inhibit the infiltration of CD4+ and CD8+ cells into the tumour microenvironment (23). Colarusso *et al.* investigated the phenomenon of PD-L1 expression in platelets in patients treated with atezolizumab (23). The presence of high levels of platelets PD-L1 (pPD-L1) was associated with up-regulation of genes involved in the organisation of the extracellular matrix and tumour immunosuppression. *In vitro* inhibition of pPD-L1 by atezolizumab-induced CXCL4 release, was accompanied by higher levels of TGFβ during the period of unresponsiveness to immunotherapy, while levels of CD16, CD32 and CD64 increased significantly. Patient survival was correlated with pPD-L levels. Data suggest that patients with stage IV NSCLC characterised by high pPD-L1 have longer PFS because blocking pPD-L1 by atezolizumab avoids promoting an immunosuppressive environment mediated by T cells (23). Thus, it appears that platelets play an important, multipotential role in modelling the tumour microenvironment and may be relevant for the use of immune checkpoint inhibitors. In our study, platelets did not have an impact on PFS or OS, while a high baseline PLR was an independent negative prognostic factor. It should also be noted that elevated values of NLR and PLR, together with thrombocitosis are among the variables included in the prognostic indices for immunotherapy [along with factors such as the presence of secondary liver lesions, elevated C-reactive protein (CRP), or lactate dehydrogenase (LDH) activity] (24-28).

Although NLR and PLR are a simple tool, it is challenging to indicate the best cut-off point. Most authors use the median to divide patients into groups with high and low NLR and PLR values. These values vary between studies, ranging from 3 to 6 for NLR and 180 to 260 for PLR, making it difficult to introduce in clinical practice as a reproducible parameter (29-33). In our study, as mentioned above, the medians were 3.86 and 193 for NLR and PLR, respectively. It is likely that the dynamics of the indices observed several weeks after the start of immunotherapy may also be important (34,35).

Our study has several limitations. First, the nature of

this analysis is retrospective, which could have introduced potential bias and confounding factors, but this two-centre study included all consecutive patients with NSCLC treated with nivolumab over a defined time interval. Furthermore, the status of the biomarker, mainly the expression of PD-L1, was only known in part of the population and could not be a reliable variable in the multivariate analysis. Similarly, the molecular profile of the patients, including *KRAS*, *STK11*, *KEAP*, and other pathogenic variants, was not routinely evaluated, and we did not include these variables in the analysis.

Conclusions

Based on the results of the present study and the data available in the literature, it can be concluded that the two parameters studied, NLR and PLR, can help assess the prognosis of patients receiving immunotherapy. Moreover it appears that they may also serve as independent prognostic factors for PFS and OS (14,36). Theye are not only predictors of survival parameters, but also estimates the likelihood of response to the treatment. Therefore, they help identify patients at high risk for early disease progression (37). However, it should be emphasised that these indices only include three cell types, neutrophils, lymphocytes, and platelets, whereas the inflammatory process in the body of a cancer patient is a process that involves many cellular elements and the cytokines and chemokines produced by them. It should also be borne in mind that the value of NLR or PLR is influenced by numerous clinical factors related to the patients, such as sex, age, smoking history, tumour malignancy, etc. Therefore, work on the use of systemic inflammation indices definitely needs a thorough validation and evaluation of their usefulness in prospective analyses.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The research was approved by the Bioethics Committee of the Medical University of Lublin (No. KE-0254/95/2018). Informed consent was obtained from all patients.

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