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Retrospective evaluation of the "neutrophil-lymphocyte ratio" (NLR) in patients affected by locally advanced unresectable stage III NSCLC treated with Durvalumab within the Italian expanded access program (EAP): results of the neutrality trial

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ABSTRACT

Background: Very little is known regarding the clinical value of inflammatory blood markers, such as NLR, Systemic Immune Inflammation (SII), derived NLR (dNLR) and Lung Immune Prognostic Index (LIPI) in stage III NSCLC patients treated as per PACIFIC regimen.

Methods: Neutrality trial (ESR-19–20410) is a retrospective multicentric study aimed at assessing the clinical impact of these blood inflammatory indexes on the clinical outcomes of such population. Unresectable stage III NSCLC patients were enrolled in two cohorts: the Durvalumab one, encompassing 94 patients treated within the Italian EAP, and the historical one, including 96 patients treated with radio-chemotherapy alone. Blood count tests were recorded at established time points from start of treatment.

Results: In the Durvalumab cohort, baseline NLR $\geq$5 significantly correlated with PFS (HR 1.93, 95% CI 1.12–3.30, $p < 0.017$; median 38.2 vs 21.4 months for NLR<5 and $\geq$5, p 0.015). The dNLR at baseline was also significantly correlated with PFS, with an HR of 2.14 (95% CI 1.14–4.02, $p = 0.018$; median 35.6 vs 18.7 months for dNLR<3 vs $\geq$3, $p = 0.016$). The median PFS of the good prognostic LIPI index group was significantly better than the intermediate group (p-value < 0.004), and the poor group (p-value < 0.039). In the historical cohort, SII correlated significantly with PFS when considered as a continuous variable (HR for each increment by 1: 1.02, 95% CI 1.01–1.03; p 0.007).

Conclusion: Neutrality trial confirmed the potential prognostic role of blood inflammatory indexes in patients with unresectable stage III NSCLC treated as per PACIFIC regimen.

Introduction

Many studies have investigated the role of inflammation and immune system cells in the tumorigenesis of solid tumors. It is well established that the tumor microenvironment (TME) plays a dual role, being involved both in antitumor processes and in tumor-promoting functions. The TME is a dynamic stromal tissue composed of fibroblasts, vascular cells, and immune cells, all of which interact with tumor cells, fostering their development and progression [1]. In addition, cancer steam cells can regulate antitumor immunity by expressing immune checkpoint molecules or by secreting soluble factors that contribute to immune evasion, with glycolysis being one of the fundamental processes in modulating immune activity in TME [2–4]. Circulating inflammatory cells may reflect the host's ability to modulate the TME and may also act as a surrogate of the immune response occurring within the tumor bed. Increasing evidence has demonstrated that targeting TME could improve tumor infiltration of lymphocytes and its combination with immunotherapy is a promising treatment strategy [5]. Based on these observations, several therapeutic approaches involving immune system cells have been developed, including immune checkpoint inhibitors, cancer vaccines, bispecific antibodies, and chimeric antigen receptors [6,7]. In this scenario blood-derived inflammatory markers may represent valuable prognostic indicators for survival outcomes in cancer patients and, if confirmed to have predictive value, could also be employed to guide personalized treatment strategies.

Several retrospective studies have examined the relationship between the neutrophil-to-lymphocyte ratio (NLR) and clinical outcomes, showing that elevated NLR is associated with worse overall survival (OS), cancer-specific survival, and disease-free survival (DFS) across a wide range of solid tumors [8,9]. Non-small cell lung cancer (NSCLC) is the most common worldwide cancer disease, with an incidence of >2 million cases per year and it remains the leading cause of cancer-related mortality [10]. In advanced NSCLC, elevated NLR has already been identified as an independent prognostic factor for poor outcomes in patients treated with anti–PD-1 or anti–PD-L1 antibodies, as well as in patients with EGFR mutations treated with specific tyrosine kinase inhibitors [11–13]. However, limited evidence is available concerning the prognostic significance of NLR in unresectable locally advanced NSCLC (LA-NSCLC) treated with radio-chemoradiotherapy (RT-CHT), and even fewer data exist on its role in patients subsequently treated with immunotherapy according to the PACIFIC regimen [14]. Of note, other inflammatory indexes have been investigated for NSCLC. Among them, the systemic inflammation index (SII), calculated as NLR multiplied by platelet count, has been shown to represent an independent prognostic marker of poor outcome in stage III NSCLC [15]. More recently, also the derived NLR (dNLR), defined as neutrophils/(leukocytes-neutrophils), and the lung immune prognostic index (LIPI), derived from the combination of dNLR and lactate dehydrogenase (LDH), showed to correlate with outcome in advanced NSCLC [16–19].

The initial aim of the Neutrality trial was to investigate the correlation between NLR, SII and clinical outcomes separately in two cohorts of patients with unresectable LA-NSCLC, one being treated per standard of care with RT-CHT before the introduction of maintenance durvalumab, and the other one as per Pacific regimen within the Italian Expanded Access Program (EAP).With the emergence of additional inflammatory indexes, dNLR and LIPI were also included in the analyses.

Materials and methods

Study design

Neutrality trial (ESR-19–20,410) is a retrospective multicentric observational no profit study. It received unconditional support from AstraZeneca. Data were reported in a large database, and the study received the approval of the Ethic Committee of the promoting center of

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Florence (approval number 18,350_oss) and subsequently of all the other ethical committees of the involved centers. Written informed consent was obtained from each participating subject in the study. Given the retrospective nature of the study, informed consent was also waived by the Ethic Committee of the promoting center regarding those subjects who were impossible to be reached at the time of data collection.

Patients

Two cohorts of patients were enrolled. Cohort A included patients with unresectable LA-NSCLC who were treated with durvalumab according to the PACIFIC regimen within the Italian Expanded Access Program (EAP). Cohort B included patients treated with radical RT-CHT alone, before the PACIFIC regimen became the standard of care in clinical practice.

Variables

For Cohort A, complete blood counts were collected at baseline, prior to the initiation of durvalumab, and subsequently at weeks 8, 16, 24, 32, 48, and 56 of treatment. For Cohort B, blood test results obtained before and after RT-CHT were considered. In this group, post RT-CHT exams were performed within 10 days from the end of concomitant treatment, or within 10 days of the last treatment delivered in case of sequential modality.

Statistical analysis

Cox proportional hazards regression models were applied to investigate the association between baseline values of NLR, SII (× 100,000), dNLR, and LIPI with OS and progression-free survival (PFS). The cut-off values were defined as follows: 5.0 for NLR (most commonly reported in the literature) and 3.5 for NLR (most representative of our cohort); 12 for SII (associated with the highest hazard ratio in our dataset); and 3 for dNLR (associated with the highest hazard ratio in our dataset). To generate these cut-offs, repeated analyses at different thresholds (the increment being 0.5, i.e. at 1.0, 1.5, etc.) were performed and the value producing the highest HR was picked up. Additional models were fitted by considering quartiles of these variables or by entering them as continuous values. LIPI was classified into three categories according to the definition by Aldea et al [20] and entered as such in the models. Finally, we fitted additional models by treating NLR, SII, dNLR, and LIPI as time-varying covariates thereby incorporating all available measurements, using the same predefined cut-offs. All statistical analyses were performed with Stata software (version 17.0). All p-values were two-sided, and statistical significance was set at $p < 0.05$. No comparative analyses of the impact of these biomarkers between the two patient groups were planned, given the retrospective nature of the study and the substantial differences in treatment era and clinical context.

Results

Patients' characteristics

A total of 96 patients in Cohort A and 94 patients in Cohort B were enrolled from 35 Italian Oncology Centers. Median follow-up, calculated using the reverse Kaplan-Meier, was 52.2 months (interquartile range 28.1–70.6 months, range 3.6–108.1 months) for Cohort A and 48.8 months (interquartile range 41.3–52.3, range 7.2–66.4 months), respectively. In Cohort A, the majority of patients were male (64.5 %) and current or former smokers (88 %), with a median age of 68 years (range 44–83 years). Adenocarcinoma was the predominant histology (56 %). PD-L1 expression was 1–49 % in 43 % of cases and ≥50 % in 31 %. Fifty percent of patients presented with stage IIIB disease. Concomitant RT-CHT was administered in 51 % of cases, while 49 % received sequential RT-CHT. Radiotherapy was most commonly delivered at a dose of 60 Gy in 30 fractions (76 %, $n = 73$). Five patients (5 %) received 66 Gy in 33 fractions, while the remaining patients received a fractionated dose below 60 Gy (ranging from 50 to 57 Gy). The median interval from completion of radiotherapy to the initiation of durvalumab was 60 days (range 14–181 days). Most patients (60 %) began maintenance immunotherapy within 30–90 days after radiotherapy. Population in Cohort B was similar to Cohort A, with 70 % of men (66 patients), 91 % of smokers and a median age of 65 years (range 42–84 y). Adenocarcinoma accounted for 53 % of cases, and 47 % had stage IIIB disease. Concomitant RT-CHT was performed in 59 patients (63 %). The most frequently prescribed radiotherapy regimen was 60 Gy in 30 fractions (59 %), followed by 66 Gy in 33 fractions (25 %); other delivered doses of RT ranged between 74 and 44 Gy. Patient and treatment characteristics of both cohorts are reported in Table 1.

Durvalumab cohort

Correlation with PFS

For baseline NLR, using a cut-off of 5, a significant difference in PFS was observed in favor of patients with NLR < 5 [HR 1.93, 95 % CI 1.12–3.30; $p = 0.017$]. Median PFS was 38.2 months for patients with NLR < 5 versus 21.4 months for patients with NLR ≥ 5 ($p = 0.015$). When a cut-off of 3.5 was applied, no statistically significant difference was found [HR 1.35, 95 % CI 0.80–2.28; $p = 0.267$], although a positive trend was noted for the NLR < 3.5 group (median PFS 38.2 vs 26.3 months; $p = 0.265$).

Table 1
Patients and treatments characteristics. SCC, squamous cell carcinoma.

	Cohort A (Durvalumab) Patients $n = 96$ (%)	Cohort B (radio-chemotherapy) Patients $n = 94$ (%)
Sex		
M	62 (64.5)	66 (70)
F	34 (35.5)	28 (30)
Smoke		
Yes	85 (88)	85 (90)
No	9 (12)	9 (10)
Age years		
Median	68	65
Range	44–83	42–84
Histology		
Adenocarcinoma	54 (56)	49 (52)
Squamocellular	39 (41)	39 (41)
Others	3 (3)	6 (7)
PD-L1 Expression		
0	12 (12.5)	11 (12)
1–49	41 (43)	15 (16)
≥ 50	30 (31)	8 (8)
Not tested	13 (13.5)	60 (64)
Stage Disease		
IIIA	35 (36.5)	39 (41)
IIIB	48 (50)	44 (47)
IIIC	13 (13.5)	11 (12)
ECOG PS		
0	59 (61.5)	60 (64)
1	35 (37.5)	34 (36)
2	1 (1)	0
Radiotherapy		
Concomitant	49 (51)	58 (62)
Sequential	47 (49)	36 (38)
Total dose		
60 Gy	73 (76)	56 (59)
66 Gy	5 (5)	24 (25)
60–66 Gy	4 (4)	1 (1)
< 60 Gy	14 (15)	12 (14)
74 Gy	0	1 (1)
Time to		
Durvalumab	16 (17)	-
< 40 days	58 (60)	
40–90 days	22 (23)	
> 90 days		

When modeled as a continuous variable, baseline NLR was significantly associated with worse PFS, with an HR of 1.07 per unit increase (95 % CI 1.00–1.14; $p = 0.040$). However, when treated as a time-varying variable, NLR was not significantly associated with PFS. Using the cut-off of 5, HR was 1.53 (95 % CI 0.90–2.60; $p = 0.120$), and using the cut-off of 3.5, HR was 1.10 (95 % CI 0.65–1.85; $p = 0.728$).

Baseline SII, considered as a continuous variable, was also significantly associated with worse PFS [HR 1.02 per unit increase, 95 % CI 1.00–1.03; $p = 0.030$]. When analyzed with the cut-off of 12, the HR for PFS was 1.34 (95 % CI 0.74–2.42; $p = 0.334$). Median PFS was 35.6 months for patients with SII < 12 compared with 21.4 months for patients with SII ≥ 12, a trend toward significance ($p = 0.077$).

Baseline dNLR significantly correlated with PFS. Using a cut-off of 3, higher values were associated with worse PFS [HR 2.14, 95 % CI 1.14–4.02; $p = 0.018$]. As a continuous variable, dNLR remained significant, with an HR of 1.19 per unit increase (95 % CI 1.02–1.38; $p = 0.023$). Median PFS was 35.6 months in the dNLR < 3 group and 18.7 months in the dNLR ≥ 3 group ($p = 0.016$).

Although LDH values were available only for a limited number of patients, LIPI classification showed significant prognostic value for PFS. Compared with the good prognostic group, the intermediate group had an HR of 2.64 (95 % CI 1.37–5.08; $p = 0.004$) and the poor group an HR of 2.88 (95 % CI 1.05–7.85; $p = 0.039$). Median PFS was 17.4 months in the poor group, 26.3 months in the intermediate group, and not reached in the good group ($p = 0.007$). When analyzed as a time-varying variable, LIPI retained prognostic significance: HR 1.97 (95 % CI 1.03–3.77; $p = 0.040$) for intermediate versus good, and HR 2.83 (95 % CI 1.06–7.55; $p = 0.037$) for poor versus good. Results for PFS are reported in Fig. 1.

Correlation with OS

A trend toward correlation with OS was observed, but statistical significance was not reached (Fig. 2). At baseline, using cut-offs of 5 and 3.5, no significant differences in OS were detected [HR 1.56, 95 % CI 0.85–2.89; $p = 0.154$ and HR 1.58, 95 % CI 0.87–2.87; $p = 0.131$, respectively]. Even when considering baseline NLR as a continuous variable, no impact was reported in OS: HR was 1.03 (CI 0.96–1.11, p-value 0.357). Similarly, when considered as a time-varying variable, NLR did not significantly correlate with OS [HR 1.36, 95 % CI 0.74–2.51; $p = 0.323$ for cut-off 5; HR 1.26, 95 % CI 0.70–2.82; $p = 0.438$ for cut-off 3.5]. Other inflammatory indexes (SII, dNLR, LIPI) did not show significant correlation with OS.

Historical cohort

In contrast to the durvalumab cohort, in the RT-CHT–only group, the only significant correlation identified was between SII and PFS when considered as a continuous variable [HR 1.02 per unit increase, 95 % CI 1.01–1.03; $p = 0.007$]. No correlation was observed when using the cut-off of 12, either for PFS or OS. Similarly, NLR, dNLR, and LIPI, analyzed either as categorical or continuous variables, did not show any significant association with PFS or OS.

Discussion

In the multicenter Neutrality trial, we evaluated the prognostic value of peripheral blood inflammatory markers, including NLR, dNLR, SII, and LIPI, on PFS and OS in patients with unresectable LA-NSCLC, with a specific focus on those treated with durvalumab as maintenance therapy after RT-CHT. In addition, we investigated whether dynamic changes in these indexes during immunotherapy could influence their prognostic significance. Parallel analyses were performed on a historical cohort of LA-NSCLC patients treated before the introduction of durvalumab, collected from the same participating centers.

Our series demonstrated that NLR, dNLR, SII and LIPI correlate significantly with PFS in patients treated according to Pacific regimen; only a trend not reaching significance, was found relatively to OS, thus probably being explained by the small number of deaths recorded, reducing the statistical power of survival analyses. On the other hand, no such impact was demonstrated in the historical cohort of NSCLC patients treated before the advent of maintenance Durvalumab.

Several retrospective studies and meta-analyses analyzed the prognostic role of NRL, SII, dNLR and LIPI in NSCLC, but their definitive clinical utility remains under investigation. NLR has been recognized as a prognostic factor since the pre-immunotherapy era and has been confirmed in metastatic disease following the introduction of PD-1/PD-L1 inhibitors, where higher NLR values correlate with worse outcomes, reflecting neutrophilia and/or lymphopenia [21]. Since inflammatory markers are generally elevated in advanced disease, most evidence derives from metastatic cohorts, while non-metastatic patients have been less frequently studied [22]. In our study, a baseline NLR cut-off of 5 identified patients with significantly worse PFS (HR 1.93), with median PFS of 21.4 versus 38.2 months, whereas lower cut-offs failed to achieve significance. These findings are consistent with prior prospective studies, such as one trial reporting worse OS in patients with NLR > 5 (HR 1.6; $p = 0.007$) [23]. Our results align with this, with an HR of 1.56 for OS when using the same cut-off, although not statistically significant. It should be also noted that even though such results were validated in a stage-adjusted analysis, the sub-analysis on stage III patients failed to find any correlation between inflammatory markers and survival. They also reported that NLR measured at later time points was not prognostic, suggesting that baseline values have the greatest significance, while subsequent assessments may be confounded by treatment-related effects. This observation is consistent with our findings, in which NLR modeled as a time-varying covariate was not predictive.

Another retrospective study from Thor et al. provided slightly different results, evaluating only stage III NSCLC patients treated with RT-CHT and durvalumab. Even though the authors didn't use a pre-specified NLR cut-off, pre-treatment NLR considered as a continuous variable was strongly correlated with PFS, HR 1.09, $p = 0.0001$ [24], comparable to our HR of 1.07. They also reported that NLR measured at later time points was not prognostic, suggesting that baseline values

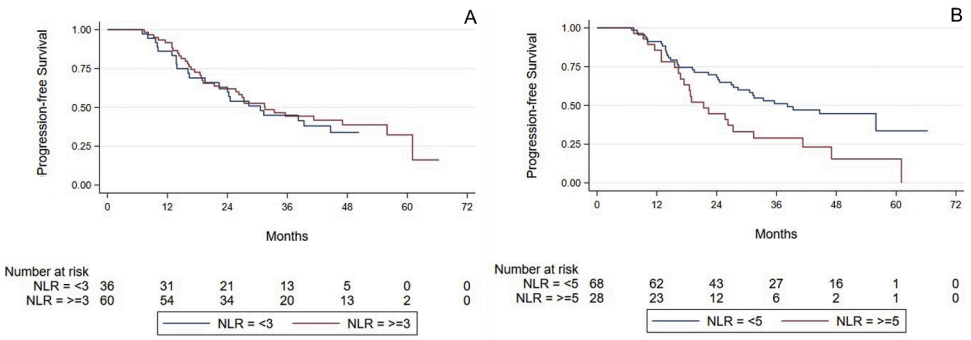

Fig. 1. Correlation between Progression-Free Survival and baseline NLR with cutoffs at 3 (A) and 5 (B). NLR, neutrophil to lymphocyte ratio.

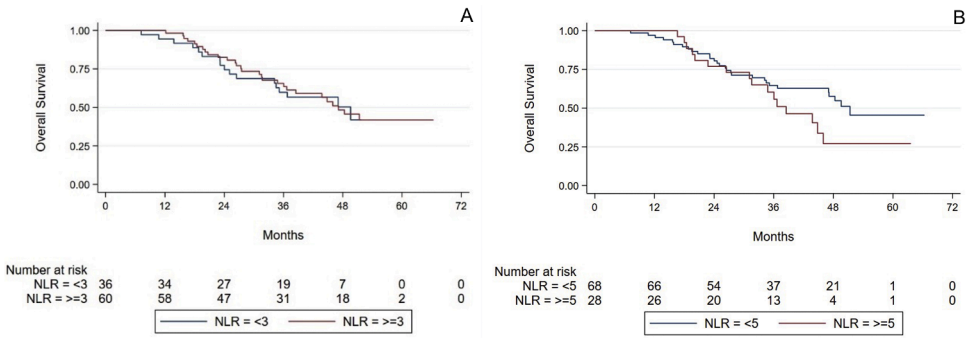

Fig. 2. Correlation between Overall Survival and baseline NLR with different cutoffs, at 3 (A) and 5 (B). NLR, neutrophil to lymphocyte ratio.

have the greatest significance, while subsequent assessments may be confounded by treatment-related effects. This observation is consistent with our findings, in which NLR modelled as a time-varying covariate was not predictive.

When restricting analyses to locally advanced disease, associations between NLR and OS are less robust compared with the metastatic setting. As said, in our study we found only a non-significant trend correlating NLR and OS, which could be partially explained by the small number of death events reported in our series, that could have affected the power of the statistical analysis. This finding is consistent with other reports. Colomb et al. identified a threshold of 2.94 by ROC analysis in two retrospective stage III NSCLC cohorts treated with RT-CHT and durvalumab, but pre-immunotherapy NLR values failed to significantly correlate with OS [25]. Interestingly, absolute lymphocyte count demonstrated stronger prognostic value, suggesting that lymphocyte depletion, rather than neutrophilia, may be more relevant in reflecting systemic inflammation.

In metastatic NSCLC, however, robust data consistently support the prognostic value of NLR, even if there is no consensus on the best cutoff NLR value to be considered. Derman et al. analysed chemotherapy-naïve patients treated with first-line platinum doublets and confirmed NLR > 5 as a negative prognostic factor for both OS and PFS [26]. The threshold used was 5 as in our trial, and significance was obtained both for OS and PFS during therapy, at 6 and 12 months.

Similarly, Petrova et al. demonstrated that NLR > 5 prior to second-line immunotherapy independently predicted poor OS (HR 8.09; $p = 0.001$) [12].

These studies together with other systematic reviews and meta-analysis [11,12,27] demonstrated the correlation with worse OS and PFS for higher NLR, with 5 remaining the most frequently adopted threshold.

Regarding dNLR, our study confirmed its prognostic value for PFS, both as a continuous variable and with a cut-off of 3. Literature supports these findings, particularly the retrospective studies by Zhang and Yang [28,29] as major studies in this setting. Their retrospective trials demonstrated that dNLR correlates both with OS and PFS in metastatic NSCLC patients. Specifically, they found statistical significance using the same cutoff of 3, with a HR for PFS of 1.30 and 1.72 in the two works, respectively.

As for the other indexes, also for LIPI, the strongest evidence again derives from metastatic disease. One of the widest analyses in this setting derives from subgroups of patients enrolled in the IMpower150 trial. In this study, NSCLC metastatic patients were randomly assigned to receive atezolizumab plus carboplatin plus paclitaxel, bevacizumab plus carboplatin plus paclitaxel, or atezolizumab plus bevacizumab, carboplatin and paclitaxel every 3 weeks for four or six cycles, followed by maintenance therapy with atezolizumab, bevacizumab, or both. The trial demonstrated that the addition of atezolizumab to bevacizumab plus chemotherapy significantly improved progression-free survival and overall survival among patients with metastatic non-squamous NSCLC, regardless of PD-L1 expression and EGFR or ALK genetic alteration status [30]. Hopkins et al [31] considered patients receiving chemotherapy plus atezolizumab and plus atezolizumab and bevacizumab from Impower150 and found that good and intermediate vs poor LIPI patients had worse OS (HR 2.16 and 5.28 p-value 0.0001, for intermediate and poor, respectively) and PFS (HR 1.47 and 3.02 p-value 0.0001, for intermediate and poor, respectively).

These results are furthermore supported by meta-analyses and pooled analyses. It is demonstrated that the gain in survival is more evident during immunotherapy treatment than during chemotherapy [32] and in general the improvement along the LIPI subgroups increases exponentially. In the work of Jianhua Xiea et al [33], the OS in the 3 prognostic subgroups (good-intermediate-poor) was 34 months vs 10 months vs 3 months, and the PSF was 6 months vs 3 months vs 1 month, respectively. These results confirm what was demonstrated in our study, even if the trend was proved only for PFS, while the significance for OS was lacking due to the few events observed and data available for this index. Furthermore, the evidence of a benefit when considering the LIPI as a time-varying variable during treatment, is confirmed in literature [34], in accordance with our findings. In the work of Xiong et al [34], for the LIPI index obtained after the second cycle of therapy, there was an advantage of the good prognostic subgroup over the intermediate and poor groups for PFS. To note, from all these analyses only a prognostic value for LIPI could be proven, without the evidence of a predictive value [20].

Data on SII in NSCLC are more limited. A large Chinese meta-analysis reported that higher SII values were associated with worse OS (HR 1.88; $p = 0.001$) and PFS (HR 2.50; $p = 0.014$) across stages I–IV [35]. Similar findings were described by Huang et al., who reported HRs of 1.75 for OS and 1.61 for PFS, although no universal cut-off was established [36]. Our findings are consistent, as baseline SII considered as a continuous variable was significantly associated with PFS.

Except for continuous increases of SII with respect to PFS, no other correlation for any clinical outcome with any inflammatory biomarker was found in our Cohort B. Even though evidence from metastatic series suggest, as already mentioned, a prognostic role for NLR in chemotherapy treated stage IV patients [26], it should be considered that, again, data reported in this setting is not homogenous. A multicentric British retrospective study of stage I-III NSCLC selected for being treated with curative-intent RT showed that only absolute lymphocyte count correlated with PFS, while NLR analysis failed. About OS, in contrast with what discussed in series with the use of Durvalumab, NLR and absolute lymphocyte post-radiotherapy performed best in identifying patients at a higher risk of dying at 2 years, with higher HR and lower p-values [37]. Moreover, it should be noted that even though an adjusted analysis for confounding factors was executed, no per stage subgroup analysis was performed, so the final result can be driven by the lower stages considered in comparison to our stage III cohort.

Other similar retrospective studies showed instead correlation with PFS and OS and NLR at pre-, post- treatment and with its differential value [36], while in another post-hoc analysis of a phase III trial testing different chemotherapy regimen, the prognostic value for NLR was

confirmed and for the absolute lymphocyte count was not [38].

This heterogeneity of outcomes is more evident especially when considering retrospective studies as ours, as pointed out in the metanalysis from Yin et al [39].

The available data, added to ours, highlight the need for a careful prospective evaluation of such markers in selected populations to provide a better understanding of the clinical factors that may influence their reliability.

In our cohort B, SII considered as continuous variable correlated significantly (p-value 0.007) with PFS. Regarding published literature, the same considerations made for NLR can be made, with concordant yet heterogenous results, having some retrospective series significantly correlating baseline SII with OS and not as clearly with PFS [40], others finding out that the change between pre- and post-treatment SII correlates better with both PFS and OS than single pre- or post- treatment values [41]. Analogously, a recent metanalysis confirmed the same results, but with a large heterogeneity in reported data to be noted [42].

Finally, to try to explain the different significance of our results between cohort A and B, it could be argued that such markers are more capable of identifying good and bad prognosis groups when immunotherapy is deployed. This fact can be explained considering that these biomarkers depict an inflammatory state not only playing a role in tumor growth and aggressiveness [43], but also interacting with and reflecting the tumor microenvironment potentially altering its responsiveness to immunotherapy stimulation [44]. Unfortunately, a direct comparison of how the addition of immunotherapy influences the prognostic impact of peripheral inflammatory markers is lacking in literature and is not possible in our study, even if a possible predictive role of these markers for the use of Durvalumab emerged from our results.

The study has several limitations, primarily related to its retrospective design, the limited number of patients, and the relatively low number of events, which reduced the statistical power for OS analyses. Furthermore, mutational status was not available, preventing evaluation of potential interactions with molecular subgroups.

Despite this, it should be noted that our study succeededed in collecting a homogenously selected, multicentric, real-word data, testing two different III stage NSCLC cohorts from the same centers, treated with or without immunotherapy, for multiple peripheral inflammatory markers at the same time, which gives consistence to the data collected and to the results provided, even if it is to be acknowledged that the study was not powered to provide direct comparisons between the two cohorts, but rather to investigate how such biomarkers can impact in these two different real-world scenarios.

Conclusions

Our data confirm that peripheral inflammatory biomarkers have potential prognostic value in unresectable stage III NSCLC treated with durvalumab following RT-CHT, according to the PACIFIC regimen. In our series, elevated NLR was significantly associated with worse PFS and demonstrated a trend toward poorer OS. Other emerging indexes, including dNLR, SII, and LIPI, also showed potential prognostic relevance for PFS.

At present, insufficient evidence exists to establish a predictive role for these biomarkers. Therefore, further prospective studies are warranted to validate these findings and to optimize the use of these simple and easily obtainable markers in guiding prognosis, patient stratification, and clinical decision-making.

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CRediT authorship contribution statement

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Vieri Scotti reports that unconditional financial support for the trial was provided by AstraZeneca Pharmaceuticals LP. Alessandro Inno reports a relationship with AstraZeneca PLC that includes: board membership and travel reimbursement. Alessandro Inno reports a relationship with Amgen Inc that includes: board membership and travel reimbursement. Alessandro Inno reports a relationship with Merck Sharp & Dohme UK Ltd that includes: board membership. Alessandro Inno reports a

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