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ORIGINAL ARTICLE



# Effect of systemic inflammation biomarkers on overall survival after lung cancer radiotherapy: a single-center large-cohort study

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**ABSTRACT**

**Introduction:** Recent studies suggest that immune-related cells can be recruited for anti-tumor functions as well as tumor progression and the interplay between systemic inflammation and local immune response may play a major role in the development and progression of various cancers including lung cancer. Inflammatory markers, such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) can be used as surrogate biomarkers of host immune status. In this work, associations between neutrophils, lymphocytes, platelets, NLR, PLR, SII and overall survival (OS) are investigated in two cohorts of non-small cell lung cancer (NSCLC) patients treated with fractionated radiotherapy (RT) and stereotactic body radiation therapy (SBRT) and a cohort of small cell lung cancer (SCLC) patients treated with fractionated RT.

**Material and Methods:** Data from 2513 lung cancer patients were retrospectively analyzed. Baseline NLR, PLR, and SII (NLR $\times$ platelet count) were calculated from full blood test prior to RT initiation. Cox proportional hazards regression analyses were used to evaluate the association between systemic inflammation markers and known clinical factors with OS.

**Results:** The two-year OS was 42%, 63%, and 62% in the NSCLC fractionated RT, SBRT, and SCLC cohort. NLR (per 1 unit: hazard ratio [HR]: 1.04, $p < 0.05$) and SII (per $100 \times 10^9$/L: HR: 1.01, $p < 0.05$) remained the strongest independent factors of OS in multivariable Cox analyses, correcting for clinical factors in early-stage and locally advanced NSCLC and SCLC patients treated with RT.

**Discussion:** This single-center large-cohort study suggests that baseline NLR and SII are independent prognostic biomarkers associated with OS in locally advanced and early-stage NSCLC patients treated with either curative-intent fractionated RT or SBRT and SCLC patients treated with curative-intent fractionated RT. External validation is warranted to evaluate the utility of these biomarkers for patients' stratification and adapting new treatment approaches.

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Lung cancer; inflammation biomarker; SBRT; fractionated RT

## Introduction

Lung cancer is one of the most common types of cancer and the leading cause of cancer-related deaths worldwide. Non-small cell lung cancer (NSCLC) accounts for nearly 85% of all primary lung cancer and is one of the most common cancers worldwide [1]. Small cell lung cancer (SCLC) accounts for approximately 15% of all lung cancers according to histological types and is the most aggressive form of lung cancer subtypes. Radiotherapy (RT) alone or in combination with chemotherapy plays a major role in the curative-intent treatment of patients diagnosed with NSCLC and SCLC. Both cancer and patient characteristics prior to treatment and therapy-related factors affect the patients' likelihood of survival. Despite recent improvement in the management of patients with lung cancer, the risk of disease progression is high, and the majority of patients will succumb to their disease. There is therefore an urgent need to improve the treatment of this group of patients [1,2]. One of the major advances in the treatment of locally advanced NSCLC in recent years is the addition of consolidation immunotherapy after concurrent chemo-radiotherapy which has led to an unprecedented increase in median survival [3]. However, there is a lack of prognostic and predictive biomarkers of outcome, other than programmed death-ligand 1 (PDL1), which can help guide the management of lung cancer patients treated with RT with or without chemotherapy. This is particularly relevant in this new immunotherapy era.

Hematologic toxicity, resulting from therapy-induced suppression of blood cells and bone marrow is a common side effect after treatment of lung cancer with RT and chemotherapy which is known to affect outcome [4,5,6]. Among blood cells, lymphocytes are known to be more radiosensitive than, for example, neutrophils and monocytes. By utilizing image-based data mining, we recently showed that radiation delivered to the heart, lungs, and thoracic vertebrae is associated with severe lymphopenia in lung cancer patients treated with curative intent RT and is predictive of overall survival (OS) [7].

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Moreover, both the host immune system and cancer-related inflammation are thought to be associated with disease progression and prognosis of many cancers [8]. It has been well documented that an imbalance of peripheral blood leukocytes is related to systemic inflammation and that this imbalance could be quantified by the neutrophils-to-lymphocytes ratio (NLR), platelet-to-lymphocyte ratio (PLR) or the systemic immune-inflammation index (SII = NLR × platelet count) [9–14]. Specifically, elevated pre-treatment NLR has been associated with poor OS of NSCLC and SCLC patients [15–17]. In addition, systemic inflammation index (SII) is also used to evaluate response to treatment in many malignant tumors [18]. Some studies showed that higher levels of SII are associated with poorer survival outcomes in NSCLC and SCLC [19–22].

In this study, we aimed to evaluate the prognostic value of absolute neutrophil counts, absolute lymphocyte counts, absolute platelet counts, NLR, PLR, SII on OS for two cohorts of locally advanced and early-stage NSCLC patients treated with fractionated RT (with or without chemotherapy) and SBRT and a cohort of SCLC patients treated with fractionated RT (with or without chemotherapy) from a single institution. We further compared prognostic models including these biomarkers to predict survival.

## Material and methods

Data from 1582 locally advanced NSCLC patients treated with curative-intent fractionated RT (total dose of 50–55/60–66 Gy in 20/33 fractions with or without chemotherapy), 211 early-stage NSCLC treated with SBRT (total dose of 54/60 Gy in 3/5/8 fractions), and 720 SCLC patients treated with curative-intent fractionated RT (total dose of 50–55/60–66 Gy in 20/33 fractions or total dose of 45 Gy in 30 bidaily fractions with or without chemotherapy) between 2005–2020 from a single institution with available pre-RT full blood test were retrospectively analyzed. Tumor volumes were obtained from RT images to be considered in the analysis. Data on patients' characteristics were extracted from electronic patients record from a structured form at the time of first consultation at The Christie NHS foundation Trust, Manchester, UK. The project was conducted in accordance with UK information and research governance (research ethics committee reference no. 17/NW/0060).

### *Blood counts*

The last reported blood counts collected within the three months prior to initiation of treatment were taken as the baseline values. Baseline NLR and PLR were calculated by dividing pre-RT absolute number neutrophil and platelet counts by the absolute number lymphocyte counts, respectively. Baseline SII was calculated as the pre-therapy absolute platelet counts multiplied by the NLR. Neutrophil counts higher than $7.5 \times 10^9$/L was defined as neutrophilia [23].

### *Statistics*

The outcomes of the analyses were OS and defined as the interval from RT initiation until death. Patients who were still alive were censored at the final follow-up. Patients were divided into high and low biomarker value groups based on the optimal cutoff values for NLR, PLR, and SII according to receiver operating characteristic (ROC) curve and the areas under the ROC curve (AUC) for generating Kaplan–Meier curves. The prognostic value of each absolute count and biomarker was evaluated with univariable and multivariable Cox proportional hazard regression analyses. Continuous values for absolute counts as well as NLR, PLR, and SII were used in the Cox analyses. Other baseline prognostic factors considered were gender, age, performance status, histology (for NSCLC models), T stage, N stage (for NSCLC fractionated RT and SCLC models), tumor volume, treatment fractions, chemotherapy delivery (for NSCLC fractionated RT and SCLC models) to control for effect of these factors in addition to biomarkers on OS. For each cohort, six multivariable Cox regression models were established to include pre-treatment neutrophil count, lymphocyte count, platelet count, NLR, PLR, and SII once at a time (to avoid multi-collinearity) together with other prognostic factors mentioned above. Fitness of Cox survival regression models was evaluated with Concordance-index. Continuous clinical and demographic predictors were assessed for nonlinear relationship to the outcome by considering a spline with three knots. two-tailed *p*-values less than 0.05 were considered to be significant. Statistical analyses were performed in R 4.1.0 (R core team, Vienna, Austria).

## Results

In total, 2513 lung cancer patients from the three cohorts were analyzed. The median age of the patients was 68 years (range, 32–91 years) in the NSCLC fractionated RT cohort, 74 years (range, 45–92 years) in the SBRT cohort, and 67 years (range, 24–88 years) in the SCLC fractionated RT cohort. The median of OS and follow-up was 14.1 months (range, 1–149.1 months) and 35.7 months (range, 8.6–189.2 months) in the NSCLC fractionated RT cohort, 25.3 months (range, 1–92.8 months) and 59 months (range, 6.7–109.2 months) in the SBRT cohort, and 12.4 months (range, 1–141.7 months) and 50.4 months (range, 9.3–182.7 months) in the SCLC fractionated RT cohort, respectively. The 2- and 5-year OS was 42% and 17% in the NSCLC fractionated RT cohort, 63% and 23% in the SBRT cohort, and 62% and 24% in the SCLC fractionated RT cohort.

The average interval time from blood sample to start of treatment was 19.7 days (14.1) for NSCLC fractionated RT, 21.8 days (12.0) for SBRT, and 26.7 days (21.3) for SCLC fractionated RT cohort. The median values of the NLR, PLR, and SII counts were 2.9, 171.9, and $792.9 \times 10^9$/L in the NSCLC fractionated RT cohort, 3.3, 160, and $841.7 \times 10^9$/L in the SBRT cohort, and 2, 130.2, and $468 \times 10^9$/L in the SCLC fractionated RT cohort, respectively. Descriptive characteristics of

**Table 1.** Descriptive characteristics of patients and baseline blood counts for the three cohorts.

| | Non-small cell lung cancer | | | | Small cell lung cancer | |
|---|---|---|---|---|---|---|
| | Fractionated RT ($n = 1582$) | | SBRT ($n = 211$) | | Fractionated RT ($n = 720$) | |
| Variables | Levels | *n* (%) | levels | *n* (%) | levels | *n* (%) |
| Gender | Female | 708 (44.8) | Female | 102 (48.3) | Female | 433 (60.1) |
| | Male | 874 (55.2) | Male | 109 (51.7) | Male | 287 (39.9) |
| Age (year) | Mean (SD) | 67.6 (9.5) | Mean (SD) | 74.4 (8.2) | Mean (SD) | 67.2 (9.3) |
| PS | 0 | 284 (18.0) | 0 | 3 (1.4) | 0 | 109 (15.1) |
| | 1 | 854 (54.0) | 1 | 81 (38.4) | 1 | 348 (48.3) |
| | 2 | 304 (19.2) | 2 | 95 (45.0) | 2 | 214 (29.7) |
| | 3 | 74 (4.7) | 3 | 19 (9.0) | 3 | 33 (4.6) |
| | missing | 66 (4.2) | missing | 13 (6.2) | missing | 16 (2.2) |
| Smoking status | Current smoker | 328 (20.7) | Current smoker | 55 (26.1) | Current smoker | 139 (19.3) |
| | Ex-smoker | 622 (39.3) | Ex-smoker | 108 (51.2) | Ex-smoker | 219 (30.4) |
| | Life-long never | 36 (2.3) | Life-long never | 4 (1.9) | Life-long never | 6 (0.8) |
| | missing | 596 (37.7) | missing | 44 (20.9) | missing | 356 (49.4) |
| Histology | Adenocarcinoma | 634 (40.1) | Adenocarcinoma | 59 (28.0) | Small cell carcinoma | 720 (100.0) |
| | Squamous cell carcinoma | 703 (44.4) | Squamous cell carcinoma | 43 (20.4) | | |
| | NoS | 149 (9.4) | NoS | 21 (10.0) | | |
| | Large cell carcinoma | 11 (0.7) | | | | |
| | NK | 85 (5.4) | NK | 88 (41.7) | | |
| T Stage | 1 | 177 (11.2) | 1 | 133 (63.0) | 1 | 94 (13.0) |
| | 2 | 454 (28.7) | 2 | 73 (34.6) | 2 | 182 (25.3) |
| | 3 | 380 (24.0) | | | 3 | 105 (14.6) |
| | 4 | 468 (29.6) | | | 4 | 184 (25.6) |
| | missing | 103 (6.5) | missing | 5 (2.4) | missing | 155 (21.5) |
| N stage | 0 | 437 (27.6) | 0 | 211 (100.0) | 0 | 113 (15.7) |
| | 1 | 195 (12.3) | | | 1 | 68 (9.4) |
| | 2 | 627 (39.6) | | | 2 | 244 (33.9) |
| | 3 | 210 (13.3) | | | 3 | 103 (14.3) |
| | missing | 113 (7.1) | | | missing | 192 (26.7) |
| LnPTV | Mean (SD) | 5.7 (0.9) | Mean (SD) | 3.4 (0.7) | Mean (SD) | 5.7 (0.8) |
| Treatment fractions | 20 | 1173 (74.1) | 3 | 12 (5.7) | 20 | 557 (77.4) |
| | 33 | 409 (25.9) | 5 | 153 (72.5) | 33 | 61 (8.5) |
| | | | 8 | 46 (21.8) | 30 Bidaily | 102 (14.2) |
| Chemotherapy delivery | Concurrent | 365 (23.1) | | | Concurrent | 74 (10.3) |
| | Induction-Concurrent | 14 (0.9) | | | Induction-Concurrent | 66 (9.2) |
| | Induction | 624 (39.4) | | | Induction | 307 (42.6) |
| | No chemotherapy | 579 (36.6) | No chemotherapy | 211 (100.0) | No chemotherapy | 273 (37.9) |
| Interval time between blood test and start of RT (days) | Mean (SD) | 19.7 (14.1) | Mean (SD) | 21.8 (12.0) | Mean (SD) | 26.7 (21.3) |
| Lymphocyte count ($\times 10^9$/L) | Mean (SD) | 1.8 (3.1) | Mean (SD) | 1.7 (0.8) | Mean (SD) | 1.7 (0.8) |
| Neutrophil count ($\times 10^9$/L) | Mean (SD) | 5.5 (4.2) | Mean (SD) | 5.8 (2.3) | Mean (SD) | 3.9 (4.1) |
| Platelet count ($\times 10^9$/L) | Mean (SD) | 290.4 (157.9) | Mean (SD) | 265.2 (79.9) | Mean (SD) | 244.1 (151.2) |
| NLR | Mean (SD) | 4.0 (4.4) | Mean (SD) | 4.5 (5.4) | Mean (SD) | 2.6 (3.4) |
| PLR | Mean (SD) | 207.0 (160.2) | Mean (SD) | 192.8 (142.4) | Mean (SD) | 161.7 (124.7) |
| SII ($\times 10^9$/L) | Mean (SD) | 1330.3 (2109.5) | Mean (SD) | 1215.2 (1556.5) | Mean (SD) | 744.8 (1317.5) |
| Neutrophilia | 0 | 1259 (79.6) | 0 | 178 (84.4) | 0 | 646 (89.7) |
| | 1 | 323 (20.4) | 1 | 33 (15.6) | 1 | 74 (10.3) |

RT: radiotherapy; SBRT: stereotactic body radiation therapy; SD: standard deviation; PS: performance status; NoS: not otherwise specified; NK: not known; LnPTV: natural logarithm of planning target volume; NLR: neutrophil/lymphocyte; PLR: platelet/lymphocyte; SII: systemic immune-inflammation index.

patients, baseline blood counts, and potential inflammation markers are listed in Table 1.

According to ROC and AUC, the optimal cutoff point for NLR, PLR, and SII was 5.5, 244, and $1218 \times 10^9$/L in the NSCLC fractionated RT cohort, 2.6, 291.7, and $749.6 \times 10^9$/L in the SBRT cohort, and 2.2, 130, and $468 \times 10^9$/L in the SCLC fractionated RT cohort. Kaplan–Meier survival curves for high and low level of NLR, PLR, and SII, based on the optimal cutoff are presented in Figure 1. Univariable and multivariable analyses of OS were performed with known clinical factors including gender, age, performance status, histology, T stage, N stage, tumor volume, chemotherapy delivery, as well as pre-treatment neutrophil count, lymphocyte count, platelet count, neutrophilia, NLR, PLR, and SII level.

Based on the univariable analysis, gender, age, performance status, histology, T stage, N stage, tumor volume,

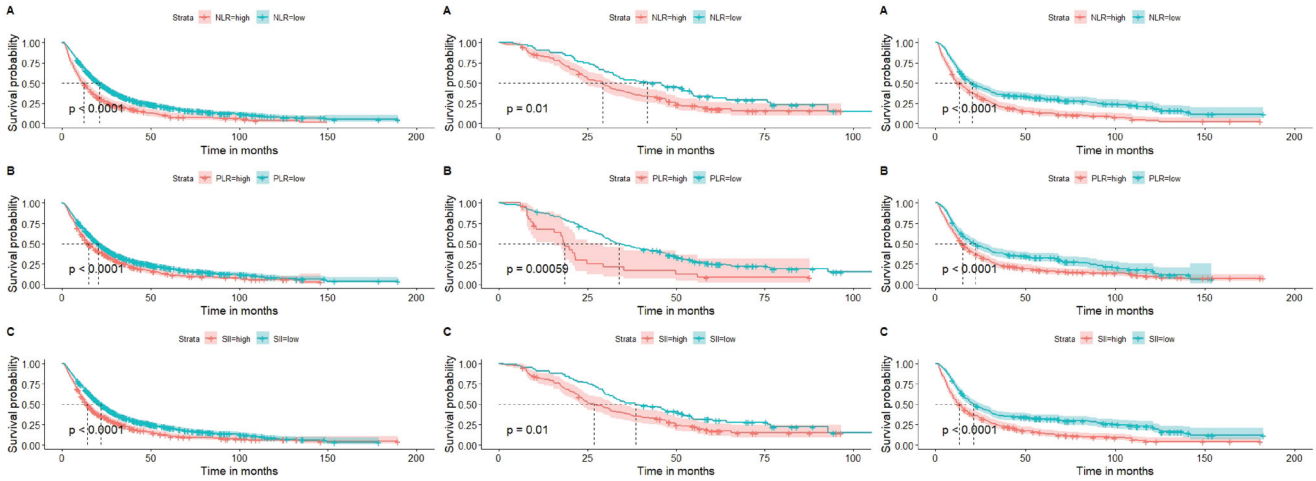


**Figure 1.** Kaplan–Meier curves for OS according to low and high level of (A) NLR, (B) PLR, and (C) SII for Left: NSCLC fractionated RT, Middle: NSCLC SBRT, and Right: SCLC fractionated RT cohorts. The optimal cutoff point for NLR, PLR, and SII was 5.5, 244, and 1218 $\times$ $10^9$/L in the NSCLC fractionated RT cohort, 2.6, 291.7, and 749.6 $\times$ $10^9$/L in the SBRT cohort, and 2.2, 130, and 468 $\times$ $10^9$/L in the SCLC fractionated RT cohort according to ROC and AUC.

treatment fractions, chemotherapy delivery, absolute neutrophil counts, NRL, PLR, SII, and neutrophilia were associated with OS in the NSCLC fractionated RT cohort (Table 2). For SBRT cohort, histology, tumor volume, NRL, PLR, and SII were associated with OS (Table 3). For SCLC fractionated RT cohort, gender, age, performance status, T stage, N stage, tumor volume, chemotherapy delivery, absolute neutrophil counts, NRL, SII, and neutrophilia were associated with OS (Table 4).

Multivariable analyses showed that NLR (per 1 unit: hazard ratio [HR]: 1.04, $p < 0.001$ for NSCLC fractionated RT, HR: 1.04, $p = 0.008$ for SBRT, HR: 1.04, $p = 0.001$ for SCLC fractionated RT) and SII (per 100 $\times$ $10^9$/L: HR: 1.01, $p < 0.001$ for NSCLC fractionated RT, HR: 1.01, $p = 0.01$ for SBRT, HR: 1.01, $p = 0.03$ for SCLC fractionated RT) were independently associated with OS across all cohorts after adjusting for gender, age, performance status, histology, T stage, N stage, tumor volume, treatment fractions, and chemotherapy delivery (Tables 2, 3, and 4). Highest model performances were obtained for multivariable Cox regressions that include NLR across all three cohorts (C-indexes were 0.72 (SE = 0.008) in the NSCLC fractionated RT, 0.73 (SE = 0.023) SBRT cohort and 0.74 (SE = 0.013) in the SCLC fractionated RT cohort). For NSCLC fractionated RT cohort and SBRT cohort, PLR was associated with OS with similar C-index to the corresponding SII (0.70 and 0.71, respectively). However, PLR from SCLC cohort did not show any significant association with OS. For NSCLC fractionated RT cohort and SCLC cohort, absolute neutrophil counts were associated with OS, however, with lower C-index compared with the above-mentioned biomarkers (0.68 and 0.70, respectively). Neutrophil counts from NSCLC SBRT cohort did not show any significant association with OS. Absolute lymphocyte and platelet counts did not show any significant associations with OS across the three cohorts. None of the tested continuous variables showed signs of nonlinearity.

## Discussion

In the present study, we investigated the association between pre-treatment neutrophil count, lymphocyte count, platelet count, NLR, PLR, SII, and OS in two cohorts of early-stage and locally advanced NSCLC and a cohort of SCLC from a single institution. We found that high pre-treatment NLR and SII values are associated with poorer OS in the three cohorts from the multivariable analyses. Multivariable Cox analyses revealed that every 1 unit increase in NLR caused a 4% increase in the risk of death in all cohorts. Moreover, each increase of 100 ($\times$ $10^9$/L) of SII was associated with a 1% increase in the hazard of death in all cohorts. Interestingly, an increase in the risk of death was similar for each biomarker across all cohorts. Despite differences in the survival of these three cohorts, given the fact that the models are corrected for the most deriving factors of survival including tumor volume, similar hazard ratios might point to the systemic effect of these biomarkers used across three cohorts. Significant associations between PLR and OS were found only in the two NSCLC cohorts.

Inflammation has been reported to increase the risk of various cancers including lung cancer. It plays a significant role in tumor development, angiogenesis, and inhibits apoptosis, thereby affecting the chance of survival of cancer patients [24]. In addition, it has been shown that neutrophils, as well as T and B lymphocytes play an important role in tumor inflammation and immune response [25].

The occurrence and development of malignant tumors are affected by both the immune system and the tumor microenvironment. The tumor microenvironment plays a crucial role in cancer progression, invasion, and distant metastasis [26]. There is abundant evidence suggesting that both neutrophils and lymphocytes are involved in tumor progression and prognosis. Lymphocytes are a critical component of human cellular immunity and are involved in anti-tumor immune responses. In particular, T lymphocytes inhibit tumor cell proliferation and metastasis *via* recognition and killing of tumor cells. Reduction in lymphocyte count reduces the anti-tumor effect of the immune system, resulting in accelerated tumor occurrence and development. It has been reported that increased lymphocyte infiltration in the tumor and its microenvironment is associated with better prognosis and response to immunotherapy in various solid tumors [27]. It

**Table 2.** Univariable and multivariable Cox regression results for overall survival in NSCLC fractionated RT cohort.

| Variable | Univariable HR (95% CI, *p*-value) | Multivariable HR (95% CI, *p*-value) |
|---|---|---|
| Gender | | |
| Female | – | – |
| Male | 1.16 (1.03–1.29, $p = 0.011$) | 1.04 (0.93–1.17, $p = 0.510$) |
| Age (per 1 year) | | |
| Mean (SD) | 1.01 (1.01–1.02, $p = 0.001$) | 1.01 (1.01–1.02, $\mathbf{p = 0.009}$) |
| PS | | |
| 0 | – | – |
| 1 | 1.31 (1.12–1.53, $p = 0.001$) | 1.17 (1.01–1.38, $p = 0.056$) |
| 2 | 1.25 (1.04–1.51, $p = 0.019$) | 1.04 (0.85–1.27, $p = 0.708$) |
| 3 | 1.54 (1.16–2.04, $p = 0.003$) | 1.38 (1.03–1.85, $\mathbf{p = 0.031}$) |
| Missing | 1.49 (1.09–2.01, $p = 0.011$) | 1.26 (0.91–1.75, $p = 0.161$) |
| Histology | | |
| Adenocarcinoma | – | – |
| Squamous cell carcinoma | 1.22 (1.08–1.38, $p = 0.001$) | 1.17 (1.03–1.33, $\mathbf{p = 0.016}$) |
| NoS | 1.29 (1.05–1.58, $p = 0.013$) | 1.39 (1.13–1.70, $\mathbf{p = 0.002}$) |
| Large cell carcinoma | 0.66 (0.27–1.58, $p = 0.349$) | 0.62 (0.25–1.50, $p = 0.285$) |
| NK | 0.87 (0.66–1.15, $p = 0.325$) | 1.13 (0.84–1.52, $p = 0.424$) |
| T Stage | | |
| 1 | – | – |
| 2 | 1.29 (1.05–1.58, $p = 0.014$) | 1.00 (0.80–1.23, $p = 0.965$) |
| 3 | 1.58 (1.28–1.95, $p < 0.001$) | 1.11 (0.88–1.39, $p = 0.384$) |
| 4 | 1.37 (1.12–1.68, $p = 0.003$) | 0.97 (0.77–1.23, $p = 0.823$) |
| Missing | 1.33 (1.00–1.77, $p = 0.051$) | 1.03 (0.70–1.51, $p = 0.900$) |
| N Stage | | |
| 0 | – | – |
| 1 | 1.21 (1.01–1.47, $p = 0.048$) | 1.11 (0.91–1.35, $p = 0.316$) |
| 2 | 1.26 (1.10–1.45, $p = 0.001$) | 1.20 (1.02–1.40, $\mathbf{p = 0.027}$) |
| 3 | 1.40 (1.16–1.68, $p < 0.001$) | 1.22 (0.99–1.50, $p = 0.066$) |
| Missing | 1.18 (0.93–1.49, $p = 0.170$) | 1.01 (0.72–1.42, $p = 0.958$) |
| LnPTV | | |
| Mean (SD) | 1.48 (1.36–1.61, $p < 0.001$) | 1.59 (1.44–1.76, $\mathbf{p < 0.001}$) |
| Treatment fractions | | |
| 20 | – | – |
| 33 | 0.71 (0.62–0.81, $p < 0.001$) | 0.85 (0.64–1.13, $p = 0.253$) |
| Chemotherapy delivery | | |
| Concurrent | – | – |
| Induction-Concurrent | 1.47 (0.82–2.63, $p = 0.191$) | 1.72 (0.95–3.13, $p = 0.075$) |
| Induction | 1.58 (1.35–1.84, $p < 0.001$) | 1.55 (1.14–2.10, $\mathbf{p = 0.005}$) |
| No chemotherapy | 1.38 (1.18–1.61, $p < 0.001$) | 1.54 (1.14–2.09, $\mathbf{p = 0.005}$) |
| Lymphocyte count (per $10^9$/L) | | |
| Mean (SD) | 0.99 (0.96–1.01, $p = 0.269$) | 0.99 (0.97–1.01, $p = 0.514$) |
| Neutrophil count (per $10^9$/L) | | |
| Mean (SD) | 1.03 (1.02–1.04, $p < 0.001$) | 1.04 (1.03–1.05, $\mathbf{p < 0.001}$) |
| Platelet count (per $10^9$/L) | | |
| Mean (SD) | 1.00 (0.99–1.01, $p = 0.981$) | 1.00 (0.99–1.00, $p = 0.228$) |
| NLR (per 1 unit) | | |
| Mean (SD) | 1.04 (1.03–1.05, $p < 0.001$) | 1.04 (1.03–1.05, $\mathbf{p < 0.001}$) |
| PLR (per 100 unit) | | |
| Mean (SD) | 1.01 (1.01–1.02, $p < 0.001$) | 1.05 (1.02–1.1, $\mathbf{p = 0.002}$) |
| SII (per $100 \times 10^9$/L) | | |
| Mean (SD) | 1.01 (1.01–1.03, $p < 0.001$) | 1.01 (1.01–1.02, $\mathbf{p < 0.001}$) |
| Neutrophilia | | |
| no | – | – |
| yes | 1.38 (1.20–1.57, $p < 0.001$) | – |

Clinical and demographic variables' HRs from multivariable analysis are reported based on the multivariable Cox model that involves NLR. *P*-values $< 0.05$ for the multivariable model are in bold.
RT: radiotherapy; HR: hazard ratio; CI: confidence interval; PS: performance status; NoS: not otherwise specified; NK: not known; LnPTV: natural logarithm of planning target volume; NLR: neutrophil/lymphocyte; PLR: platelet/lymphocyte; SII: systemic immune-inflammation index.

has also been shown that low level of lymphocyte count is associated with lymphatic invasion and recurrence of NSCLC [28].

The level of absolute neutrophil counts in circulating blood is an indicator of inflammation. Neutrophil counts act both on tumor cells and tumor microenvironment, driving or promoting tumor development [29]. Neutrophils secrete tumor growth factors, cytokines, and chemokines, including interleukin 6, 8, and 12, transforming growth factor beta, vascular endothelial growth factor, and matrix metalloproteinase, which can promote angiogenesis [10]. Moreover, tumor cells release granulocyte colony stimulating factor, which leads to an increase in the neutrophil count. Thus, a mutually reinforcing association exists between neutrophil counts and tumor cells [30].

It has been reported that baseline lymphocyte counts, neutrophil counts, and baseline neutrophilia are associated with OS in various cancer patients [23,31–34]. In the current study, no significant association was found between baseline lymphocyte counts and OS. Baseline neutrophil counts were

**Table 3.** Univariable and multivariable Cox regression results for overall survival in NSCLC cohort treated with SBRT.

| Variable | Univariable HR (95% CI, *p*-value) | Multivariable HR (95% CI, *p*-value) |
|---|---|---|
| Gender | | |
| Female | – | – |
| Male | 1.05 (0.77–1.43, $p = 0.752$) | 1.17 (0.83–1.65, $p = 0.370$) |
| Age (per 1 year) | | |
| Mean (SD) | 1.01 (0.99–1.03, $p = 0.259$) | 1.00 (0.98–1.03, $p = 0.659$) |
| PS | | |
| 0 | – | – |
| 1 | 0.77 (0.19–3.15, $p = 0.714$) | 0.57 (0.14–2.40, $p = 0.446$) |
| 2 | 0.95 (0.23–3.88, $p = 0.944$) | 0.66 (0.16–2.78, $p = 0.576$) |
| 3 | 1.34 (0.31–5.85, $p = 0.694$) | 0.98 (0.22–4.38, $p = 0.977$) |
| missing | 1.34 (0.30–6.07, $p = 0.701$) | 0.78 (0.16–3.79, $p = 0.759$) |
| Histology | | |
| Adenocarcinoma | – | – |
| Squamous cell carcinoma | 1.18 (0.75–1.84, $p = 0.471$) | 0.97 (0.61–1.56, $p = 0.916$) |
| NoS | 1.74 (1.02–2.99, $p = 0.043$) | 1.70 (0.95–3.04, $p = 0.072$) |
| NK | 0.76 (0.52–1.11, $p = 0.160$) | 0.78 (0.52–1.18, $p = 0.242$) |
| T stage | | |
| 1 | – | – |
| 2 | 1.24 (0.89–1.71, $p = 0.201$) | 0.91 (0.63–1.30, $p = 0.595$) |
| missing | 1.15 (0.36–3.63, $p = 0.812$) | 0.91 (0.25–3.28, $p = 0.889$) |
| LnPTV | | |
| Mean (SD) | 1.38 (1.09–1.73, $p = 0.007$) | 1.33 (1.01–1.75, $\mathbf{p = 0.043}$) |
| Treatment fractions | | |
| 3 | – | – |
| 5 | 1.45 (0.67–3.10, $p = 0.344$) | 1.05 (0.48–2.31, $p = 0.895$) |
| 8 | 1.04 (0.46–2.37, $p = 0.918$) | 0.66 (0.28–1.56, $p = 0.341$) |
| Lymphocyte count (per $10^9$/L) | | |
| Mean (SD) | 0.83 (0.67–1.04, $p = 0.099$) | 0.82 (0.65–1.03, $p = 0.090$) |
| Neutrophil count (per $10^9$/L) | | |
| Mean (SD) | 1.04 (0.97–1.12, $p = 0.224$) | 1.04 (0.97–1.11, $p = 0.318$) |
| Platelet count (per $10^9$/L) | | |
| Mean (SD) | 1.00 (0.99–1.00, $p = 0.636$) | 1.00 (0.99–1.00, $p = 0.565$) |
| NLR (per 1 unit) | | |
| Mean (SD) | 1.04 (1.01–1.06, $p = 0.005$) | 1.04 (1.01–1.07, $\mathbf{p = 0.008}$) |
| PLR (per 100 unit) | | |
| Mean (SD) | 1.02 (1.01–1.03, $p = 0.007$) | 1.02 (1.01–1.03, $\mathbf{p = 0.007}$) |
| SII (per $100 \times 10^9$/L) | | |
| Mean (SD) | 1.02 (1.01–1.05, $p = 0.005$) | 1.01 (1.01–1.02, $\mathbf{p = 0.010}$) |
| Neutrophilia | | |
| no | – | |
| yes | 0.96 (0.62-1.49, $p = 0.866$) | |

Clinical and demographic variables' HRs from multivariable analysis are reported based on the cox model that involves NLR. *P*-values $< 0.05$ for the multivariable model are in bold.
RT: radiotherapy; HR: hazard ratio; CI: confidence interval; PS: performance status; NoS: not otherwise specified; NK: not known; LnPTV: natural logarithm of planning target volume; NLR: neutrophil/lymphocyte; PLR: platelet/lymphocyte; SII: systemic immune-inflammation index.

associated with worse OS in multivariable Cox analyses only for locally advanced NSCLC and SCLC treated with fractionated RT.

The utility of the NLR lies in its ability to reflect the degree of inflammation in a patient's body and it has been identified as a prognostic factor of progression and survival in a series of studies. In addition to neutrophils and lymphocytes, platelets, another inflammatory cells, also play an important role in the oncogenesis, survival of metastatic cells, and cancer development [35]. SII is a new composite of the neutrophil, lymphocyte, and platelet counts in the peripheral blood and reported to be associated with prognosis in NSCLC and SCLC [18,22]. In our study, we did not identify any additional prognostic benefit of SII compared with NLR in the two cohorts of early-stage and locally advanced NSCLC and a cohort of SCLC.

Most analyses from the literature are limited by the number of patients, type, stage of the disease, number of inflammation biomarkers tested, and dichotomized value of a biomarker used in the multivariable modeling. The cutoff values of the NLR, PLR, and SII are inconsistent in the literature, thus their clinical applicability is limited. Our results based on the large dataset showed that the optimal cutoff values of the NLR, PLR, and SII are dependent on the disease type and stage. The highest cutoff values for NLR and SII were found for NSCLC fractionated RT cohort, while lowest values for NLR, PLR, and SII were for SCLC cohort. Thus, in our analyses, the impact of the NLR, PLR, and SII has been explored as a continuous explanatory variable in the multivariable analyses. To the best of our knowledge, this is the largest single-center study, investigating the effect of various systemic inflammation biomarker on OS of patients with early-stage and locally advanced NSCLC and SCLC. Our results suggest that both baseline NLR and SII are promising prognostic factors in both early-stage and locally advanced NSCLC and SCLC. Such blood biomarkers are easily obtained from routine blood tests and are cheap and convenient, however, their clinical applicability warrant further prospective studies.

There are a number of limitations in the study design including the retrospective data collection and inherent

**Table 4.** Univariable and multivariable Cox regression results for overall survival in SCLC cohort treated with fractionated RT.

| Variable | Univariable HR (95% CI, *p*-value) | HR (multivariable) |
|---|---|---|
| Gender | | |
| Female | – | – |
| Male | 1.55 (1.31–1.83, $p < 0.001$) | 1.53 (1.28–1.82, **$p < 0.001$**) |
| Age (per 1 year) | | |
| Mean (SD) | 0.99 (0.98–0.99, $p = 0.010$) | 1.00 (0.99–1.01, $p = 0.727$) |
| PS | | |
| 0 | – | – |
| 1 | 1.64 (1.28–2.09, $p < 0.001$) | 1.51 (1.17–1.95, **$p = 0.002$**) |
| 2 | 0.98 (0.74–1.29, $p = 0.875$) | 1.13 (0.83–1.54, $p = 0.428$) |
| 3 | 1.76 (1.15–2.71, $p = 0.010$) | 1.49 (0.95–2.33, $p = 0.082$) |
| missing | 2.35 (1.35–4.07, $p = 0.002$) | 2.36 (1.29–4.30, **$p = 0.005$**) |
| T Stage | | |
| 1 | – | – |
| 2 | 1.14 (0.86–1.51, $p = 0.368$) | 1.07 (0.80–1.44, $p = 0.636$) |
| 3 | 1.40 (1.03–1.91, $p = 0.033$) | 1.39 (1.01–1.93, **$p = 0.047$**) |
| 4 | 1.34 (1.01–1.77, $p = 0.039$) | 1.06 (0.79–1.43, $p = 0.693$) |
| missing | 0.60 (0.43–0.82, $p = 0.002$) | 0.55 (0.37–0.83, **$p = 0.004$**) |
| N Stage | | |
| 0 | – | – |
| 1 | 1.12 (0.80–1.57, $p = 0.513$) | 1.12 (0.79–1.59, $p = 0.509$) |
| 2 | 1.44 (1.12–1.84, $p = 0.004$) | 1.31 (1.01–1.71, **$p = 0.041$**) |
| 3 | 1.68 (1.25–2.26, $p = 0.001$) | 1.39 (1.03–1.92, **$p = 0.047$**) |
| missing | 0.84 (0.64–1.10, $p = 0.207$) | 1.52 (1.08–2.14, **$p = 0.017$**) |
| LnPTV | | |
| Mean (SD) | 1.24 (1.08–1.42, $p = 0.002$) | 1.30 (1.12–1.51, **$p = 0.001$**) |
| Treatment fractions | | |
| 20 | – | – |
| 33 | 0.75 (0.56–1.01, $p = 0.054$) | 0.70 (0.42–1.16, $p = 0.161$) |
| 30- bidaily | 0.81 (0.64–1.03, $p = 0.086$) | 0.75 (0.47–1.19, $p = 0.221$) |
| Chemotherapy delivery | | |
| concurrent | – | – |
| Induction-Concurrent | 0.89 (0.61–1.30, $p = 0.546$) | 0.92 (0.57–1.48, $p = 0.733$) |
| Induction | 1.64 (1.23–2.18, $p = 0.001$) | 1.31 (0.78–2.20, $p = 0.303$) |
| No chemotherapy | 0.85 (0.63–1.13, $p = 0.266$) | 0.88 (0.54–1.41, $p = 0.588$) |
| Lymphocyte count (per $10^9$/L) | | |
| Mean (SD) | 1.04 (0.94–1.16, $p = 0.461$) | 1.05 (0.94–1.17, $p = 0.370$) |
| Neutrophil count (per $10^9$/L) | | |
| Mean (SD) | 1.03 (1.01–1.05, $p = 0.004$) | 1.02 (1.01–1.04, **$p = 0.011$**) |
| Platelet count (per $10^9$/L) | | |
| Mean (SD) | 1.00 (0.97–1.02, $p = 0.137$) | 1.00 (0.99–1.01, $p = 0.325$) |
| NLR (per 1 unit) | | |
| Mean (SD) | 1.05 (1.02–1.07, $p < 0.001$) | 1.04 (1.02–1.06, **$p = 0.001$**) |
| PLR (per 100 unit) | | |
| Mean (SD) | 1.00 (0.99–1.01, $p = 0.122$) | 1.04 (0.99–1.05, $p = 0.229$) |
| SII (per $100 \times 10^9$/L) | | |
| Mean (SD) | 1.01 (1.01–1.02, $p = 0.001$) | 1.01 (1.01–1.02, **$p = 0.032$**) |
| Neutrophilia | | |
| no | – | – |
| yes | 1.67 (1.30–2.15, $p < 0.001$) | – |

Clinical and demographic variables' HRs from multivariable analysis are reported based on the cox model that involves NLR. *P*-values $< 0.05$ for the multivariable model are in bold.

RT: radiotherapy; HR: hazard ratio; CI: confidence interval; PS: performance status; NK: not known; LnPTV: natural logarithm of planning target volume; NLR: neutrophil/lymphocyte; PLR: platelet/lymphocyte; SII: systemic immune-inflammation index.

biases associated with its retrospective nature. Data were obtained only from a single institution which may affect statistical accuracy. In addition, owing to the inclusion of patient data from a rather large time span (15 years), there may have been a significant variation in diagnostic work-up and heterogeneity in the treatment regimens and techniques, which may affect the results. However, the use of this wide range data increases treatment variability and therewith improves the statistical power of the modeling. Another limitation of this study is the unavailability of data on infectious disease and the use of immunosuppressive agents, such as corticosteroids, which are known to reduce T lymphocyte counts or the presence of inflammatory conditions and the use of prophylactic antibiotics [36,37]. Moreover, the prognostic value of NLR and SII was found in many cancer types, indicating that they might not be a tumor-specific biomarkers.

In conclusion, the results of our study demonstrated that NLR and SII are independent prognostic blood biomarkers in patients with early-stage NSCLC treated with stereotactic body radiation therapy, locally advanced NSCLC and SCLC treated with fractionated chemo-radiotherapy. Incorporation

of NLR and SII in prognostic models could help guide the management of lung cancer patients. This could be particularly relevant in the era of immunotherapy as it may help distinguishing patients with locally advanced disease with good and poor prognosis in addition to well established biomarkers such as PDL1. Further external validations are warranted to verify the significance in clinical practice.

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No potential conflict of interest was reported by the authors.

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