



Pre-treatment systemic immune-inflammation represents a prognostic factor in patients with advanced non-small cell lung cancer

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Background: Inflammation plays an important role in pathogenesis, development and progression of lung cancer. The aim of the study is to assess the prognostic role of Systemic Immune-Inflammation Index (SII), obtained by analyzing the neutrophil, lymphocyte and platelet counts, and to design prognostic models for patients receiving first-line chemo- or targeted therapy for advanced non-small cell lung cancer (NSCLC).

Methods: We conducted an analysis on 311 patients with advanced NSCLC, treated with first line chemo- or targeted therapy till June 2015 at our Institution. Patients were stratified in two groups with SII $\geq 1,270$ (Group A) vs. SII $< 1,270$ (Group B). Progression free survival (PFS) and overall survival (OS) were estimated using Kaplan-Meier method. The best SII cutoff was identified by X-tiles program. A Cox regression model was carried out for univariate and multivariate analyses.

Results: At baseline, 179 patients had SII $\geq 1,270$ (Group A), whilst 132 had lower SII (Group B). The median OS was 12.4 months in Group A and 21.7 months in Group B ($P < 0.001$), whilst the median PFS was 3.3 and 5.2 months, respectively ($P = 0.029$). At multivariate analysis, male gender, ECOG-PS ≥ 2 and SII $> 1,270$ were predictors of worst OS, whilst IV tumor stage was only slightly significant ($P = 0.08$). Otherwise, only wild-type EGFR status and SII $\geq 1,270$ were independent prognostic factors for worst PFS.

Conclusions: Pre-treatment SII is an independent prognostic factor for patients with advanced NSCLC treated with first-line therapies.

Keywords: Lung cancer; platinum-base chemotherapy; prognosis; systemic immune-inflammation index; targeted therapy

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Introduction

Non-small cell lung cancer (NSCLC) represents approximately the 85–90% of all lung cancers. It is the leading cause of cancer related death, worldwide, in both sex and its incidence are still increasing (1). Currently, many treatment options are available for these patients. However, their prognosis remains poor, suggesting that reliable bookmakers are strongly required in order to guide treatment decisions and optimize patients' outcome.

Inflammation plays an important role in pathogenesis, development and progression of lung cancer. It has been showed that the most common chronic inflammatory lung diseases, as sarcoidosis or chronic obstructive pulmonary disease (COPD), increase the risk of lung cancer occurrence (2), whilst the chronic use of nonsteroidal anti-inflammatory drugs seems to prevent its onset (3).

Inflammatory markers, such as elevated neutrophil count and thrombocytosis, have been associated with the prognosis of NSCLC patients. Indeed, elevated neutrophil count has been correlated with poor outcome in NSCLC patients treated with chemotherapy, with an overall survival (OS) reduction of about 9 months (19.3 *vs.* 10.2 months) compared to patients with normal neutrophil count (4). In addition, NSCLC patients with preoperative thrombocytosis, platelet-to-lymphocyte ratio (PLR), neutrophil/lymphocyte ratio and prognostic nutritional index showed a significantly shorter disease-free survival (DFS) and OS (5–7). Similarly, elevated platelets count, C-reactive protein and high fibrinogen level were demonstrated as independent poor prognostic factors also in patients with advanced NSCLC (8,9).

Recently, a novel inflammatory parameter, named Systemic Immune-Inflammation Index (SII), obtained by analyzing the neutrophil, lymphocyte and platelet counts, has been investigated as a prognostic factor in patients with hepatocellular carcinoma (HCC). In this study, Hu and colleagues reported that high SII represented a prognostic indicator of poor outcome in HCC patients after curative tumor resection (10).

In this study, we investigated the prognostic role of Systemic Immune-Inflammation in patients with advanced NSCLC treated with first-line chemo- or targeted therapy.

Methods

Study population and data collection

We retrospectively collected data of patients treated

with first-line therapy for advanced NSCLC. The study population included adults (age ≥ 18 years) with histologically or cytologically diagnosis of NSCLC. All patients were treated according to EGFR mutational status with first-line chemotherapy or targeted therapy, at our Institutions between 1st May 2006 and 30th June 2015. Tumor stages were established according to the tumor-node-metastasis (TNM) criteria, using the 7th edition. Patients with IIIB and IV stage were included; patients with IIIA stage, when not eligible for curative surgery, were also included. We excluded patients receiving surgery or radiotherapy, with palliative intent, within 1 month from the start of first-line therapy or presenting factors influencing SII (see below).

First-line therapy was continued until clinical and/or radiological progression or unacceptable adverse events (AEs) or death. Follow-up was performed by physical examination, periodical laboratory analysis and computed tomography (CT) or magnetic resonance imaging (MRI) scans every 8–12 weeks.

OS was defined as the time from the start of first-line therapy to death. Disease progression was defined according to the RECIST 1.0 criteria (11). Patients with partial or complete remission or presenting stable diseases were considered as responders. Progression free survival (PFS) was defined as the time from the start of first-line therapy to progression or death. Patients without tumour progression or death at data collection time were censored at their last date of evaluation.

Peripheral blood samples were picking up 1 to 7 days before the beginning of first-line therapy. We excluded all patients without available data on pre-treatment neutrophil, lymphocyte and platelet counts, and patients with SII influencing factors, including essential thrombocythemia (ET), chronic myelogenous leukemia (CML), chronic inflammatory diseases, autoimmunity and recent therapy with granulocyte colony stimulating factor (G-CSF) or steroids. Data were collected from electronic medical records and paper charts. Patient's personal data have been secured. Our project has been approved by local Ethics Committee (ID 2019-146) and the work conforms to the provisions of in accordance with the Helsinki Declaration as revised in 2013.

Statistical analysis

PFS and OS were estimated from Kaplan-Meier curves with Rothman's 95% confidence intervals (CI). The comparison among groups was performed by the log-rank test.

Pre-treatment SII was calculated by multiplying the absolute platelet and neutrophil counts and dividing by the absolute lymphocyte count ($SII = P \times N/L$). Clinic-pathological factors potentially correlated with the patients' prognosis were estimated. The list of evaluated factors included age (≥ 70 vs. < 70 years), gender, tumor histology [non-adenocarcinoma (non-ADC) vs. ADC], stage, EGFR mutational status, Eastern Cooperative Oncology Group-Performance Status (ECOG-PS), smoking history and SII. The cut-off that best discriminated between good and poor survival was determined by the X-tile 3.6.1 software (Yale University, New Haven, CT, USA) (12).

Univariate and multivariate Cox regression analyses of potential factors affecting patients' outcome were performed. No-multicollinearity of the grouped co-variables was checked. Significance level at the univariate model for inclusion in the multivariate model was set at 0.2 (13,14). All other significance levels were set at 0.05 and all P values were two-sided. Statistical analysis was performed by MedCalc version 11.4.4.0 (MedCalc Software, Broekstraat 52, 9030 Mariakerke, Belgium).

Results

Patient characteristics

Out of 311 patients with advanced NSCLC, treated at our institution, 216 were males (69%). The median age was 68 years (range, 25–86 years). Two hundred and thirty-six patients (76%) were current or former smokers. Histology was ADC in 61%, whilst 22% had squamous carcinomas and 17% other tumor histologies. Tumor stage was III in 75 (24%) patients and IV in 236 patients (76%). First-line therapy was chemotherapy in 290 patients (93%) and EGFR-TKIs in 21 patients (7%). Patient characteristics are summarized in *Table 1*.

The median neutrophil count was $7,020/\text{mm}^3$, median lymphocyte count was $1,370/\text{mm}^3$ and median neutrophil to lymphocyte ratio (NLR) was 5.1. Absolute neutrophilia (defined as $\geq 7,500/\text{mm}^3$ in our Institution) was present in 137 patients (44%), while lymphocytopenia (defined as $< 1,500/\text{mm}^3$ in our Institution) was reported in 188 patients (60%). Thirty-four patients (11%) presented thrombocytosis (defined as $\geq 450,000/\text{mm}^3$ at our Institution).

The best SII cutoff was $\geq 1,270$ vs. $< 1,270$, as identified by X-tiles program. Patients were further shared depending on SII into two groups. One hundred and seventy-nine

patients had $SII \geq 1,270$ (Group A), whilst 132 had lower SII (Group B).

Overall survival (OS)

The median OS from first-line therapy was 16.1 months (95% CI, 13.9 to 18.6 months) in the overall population. One hundred and eighty-nine patients (61%) died during their follow-up.

The median OS was 14.4 months (95% CI, 9.5 to 15.5 months) in males and 19.6 months (95% CI, 14.4 to 27.9 months) in females ($P=0.023$). No significant difference was found between patients aged < 70 vs. ≥ 70 years (17.8 vs. 14.4 months, $P=0.165$) and between 75 non-smokers patients (19.6 months; 95% CI, 16.5 to 28.6 months) and 236 smokers (14.6 months; 95% CI, 10.8 to 16.0 months) ($P=0.406$). Otherwise, patients with ECOG-PS ≥ 2 had a significantly shorter OS compared to ECOG-PS < 2 (5.0 vs. 16.9 months, $P=0.002$).

Based on histology, the median OS was 12.7 months (95% CI, 10.3 to 16.3 months) in patients with squamous carcinoma and other histologies and 21.2 months (95% CI, 16.4 to 27.0 months) in patients with adenocarcinoma ($P=0.008$).

Moreover, the median OS was shorter in patients with neutrophilia (11.8 months; 95% CI, 9.3 to 16.3 months) compared to patients with normal neutrophil count (17.7 months; 95% CI, 14.4 to 21.4 months) ($P<0.001$). On the other hand, no significant differences were found between patients with or without lymphocytopenia (15.0 vs. 16.9 months, $P=0.207$) and with or without thrombocytosis (16.0 vs. 16.1 months, $P=0.196$).

Stratified by SII, the median OS was 12.4 months (95% CI, 9.4 to 15.7 months) in Group A and 21.7 months (95% CI, 13.3 to 27.7 months) in Group B ($P<0.001$) (*Figure 1A*). At multivariate analysis, male gender ECOG-PS ≥ 2 and $SII > 1,270$ were predictor parameters of worst OS, whilst IV tumor stage was only slightly significant ($P=0.08$). Otherwise, only wild-type EGFR status and $SII \geq 1,270$ were independent prognostic factors for worst PFS.

Considering different potential inflammation status in different histological type of NSCLC we calculated SII cut off for patients with adenocarcinomas and with squamous carcinoma, resulting respectively of 1,085 and 562.

SII was confirmed to be a prognostic factor in patients with adenocarcinomas with a mOS 32.8 months (95% CI, 27.9 to 37.6 months) in patients with $SII < 1,085$ and 19.36 months (95% CI, 17.5 to

Table 1 Patients' characteristics

Patients	Overall, 311 [%]	SII $\geq 1,270$, 179 [58]	SII $< 1,270$, 132 [42]	P value
Gender				0.9645
Male	216 [69]	124 [69]	92 [70]	
Female	95 [31]	55 [31]	40 [30]	
Age, years [range]	68 [25–86]	65 [25–83]	68 [29–86]	0.0232
ECOG				0.8473
ECOG-PS ≥ 2	21 [7]	13 [7]	8 [6]	
ECOG-PS < 2	290 [93]	166 [93]	124 [94]	
Histology				0.0004
Adenocarcinoma	189 [61]	121 [68]	68 [51]	
Squamous carcinoma	69 [22]	31 [17]	38 [29]	
Other	53 [17]	27 [15]	26 [20]	
NOS (not otherwise specified)	50 [16]	25 [14]	25 [19]	
Mixed-histology	3 [1]	2 [1]	1 [1]	
Tumor stage				0.0154
Stage III	75 [24]	36 [20]	39 [30]	
Stage IV	236 [76]	143 [80]	93 [70]	
EGFR mutation status				0.0575
Wild-type	278 [89]	164 [92]	114 [86]	
Mutated	33 [11]	15 [8]	18 [14]	
Smoking history				0.7665
Former/current smokers	236 [76]	138 [77]	98 [74]	
Never smokers	75 [24]	41 [23]	34 [26]	
Common sites of metastasis				
Lung	136 [44]	83 [46]	53 [40]	
Bone	80 [26]	56 [31]	24 [18]	
Nervous system	37 [12]	22 [12]	15 [11]	
Liver	45 [14]	29 [16]	16 [12]	
First-line therapy				
Platinum-based chemotherapy	240 [77]	148 [83]	92 [70]	
Non platinum-based	50 [16]	18 [10]	32 [24]	
EGFR-TKI	21 [7]	13 [7]	8 [6]	
Response to first-line therapy				
Partial response	109 [35]	64 [36]	45 [34]	
Stable disease	73 [24]	33 [18]	40 [30]	
Progression disease	129 [41]	82 [46]	47 [36]	

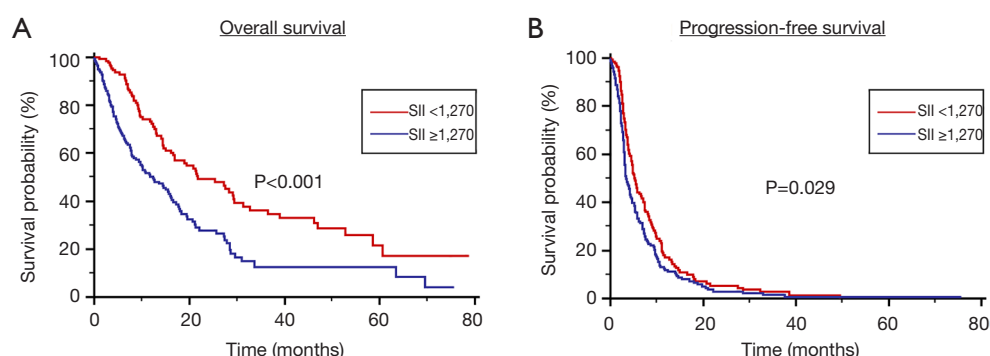


Figure 1 OS (A) and PFS (B) stratified by Systemic Immune-Inflammation Index (SII) in patients treated with first-line therapy for locally advanced or metastatic NSCLC. NSCLC, non-small cell lung cancer; PFS, progression free survival; OS, overall survival.

21.2 months) for those with SII >1,085, $P=0.0112$) and in patients with squamous carcinoma with a mOS 19.4 months (95% CI, 14.0 to 24.8 months) in patients with SII <562 and 9.5 months (95% CI, 7.4 to 11.6 months) for those with SII >562, $P=0.0219$).

Progression-free survival (PFS)

The median PFS was 4.4 months (95% CI, 3.9 to 5.1) in the overall study population, 5.4 months (95% CI, 3.5 to 8.2 months) in the 75 non-smokers and 4.2 months (95% CI, 3.6 to 4.8 months) in the 236 smokers' patients ($P=0.375$).

The median PFS was 4.0 months (95% CI, 3.6 to 4.7 months) in males and 5.4 months (95% CI, 4.4 to 6.9 months) in females ($P=0.131$). No significant difference was found between patients aged <70 *vs.* ≥70 years (4.2 *vs.* 4.6 months, $P=0.568$), ECOG-PS ≥2 *vs.* <2 (3.7 *vs.* 4.2 months, $P=0.45$), histology (squamous carcinoma *vs.* adenocarcinoma *vs.* other histologies: 3.9 *vs.* 4.6, respectively).

Furthermore, no differences in terms of median PFS were found between patients with (3.7 months; 95% CI, 3.3 to 4.5 months) and without absolute neutrophilia (4.8 months; 95% CI, 3.9 to 5.7 months, $P=0.150$). Similarly to OS, no difference was found between patients with and without lymphocytopenia (3.5 *vs.* 4.5 months, $P=0.379$) and with or without thrombocytosis (3.2 *vs.* 4.4 months, $P=0.792$).

Stratified by SII, the median PFS was 3.3 months (95% CI, 2.8 to 4.4 months) in Group A and 5.2 months (95% CI, 4.2 to 7.5 months) in Group B ($P=0.029$) (Figure 1B).

Elevated SII was confirmed also to be associated to poorer PFS in patients with adenocarcinomas with a mPFS 10.3 months (95% CI, 9.6 to 11.0) in patients with SII <1,085 and 5.8 months (95% CI, 5.2 to 6.4) for those with SII ≥1,085, $P=0.0117$, and in patients with squamous carcinoma with a mPFS 14.6 months (95% CI, 10.9 to 18.3 months) in patients with SII <562 and 3.9 months (95% CI, 2.4 to 5.8 months) for those with SII ≥562, $P=0.0452$.

Univariate and multivariate analyses

Univariate analysis showed that age (≥70 *vs.* <70 years), male gender, ECOG-PS ≥2, tumor ADC histology, tumor stage IV and SII ≥1,270 were significantly associated with worst OS (Table 2). At multivariate analysis, male gender, ECOG-PS ≥2 and SII >1,270 were predictors of worst OS, whilst IV tumor stage was only slightly significant ($P=0.088$) (Table 2).

As for PFS, univariate analysis showed that male gender, tumor stage IV, wild-type EGFR status and SII ≥1,270 significantly associated with shorter PFS (Table 3). Multivariate Cox regression analysis revealed that only wild-type EGFR status and SII ≥1,270 were independent prognostic factors for worst PFS (Table 3).

Prognostic models for OS and PFS

Based on the multivariate analysis, male gender, ECOG-PS ≥2 and SII >1,270 were significantly associated with OS.

Patients were stratified according to the absence of the 3 significant prognostic factors (39 patients, 13%), presence of 1 (137 patients, 44%) or ≥2 factors (135 patients, 43%).

Table 2 Univariate and multivariable analysis of predictors of OS in patients treated with first-line therapy for locally advanced or metastatic NSCLC

Evaluated variables	Univariate Cox regression		Multivariable cox regression	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (≥ 70 vs. < 70 years)	1.23 (0.92–1.63)	0.165	1.28 (0.95–1.72)	0.113
Gender (F vs. M)	0.68 (0.50–0.95)	0.023	0.72 (0.51–0.99)	0.047
ECOG-PS (≥ 2 vs. < 2)	2.19 (1.35–3.56)	0.002	1.84 (1.12–3.03)	0.016
Smoke status (Y vs. N)	1.17 (0.81–1.68)	0.406		
Tumor stage (IV vs. III)	1.46 (1.05–2.01)	0.023	1.34 (0.96–1.86)	0.088
Histology (non-AC vs. AC)	1.61 (1.14–2.47)	0.008	0.93 (0.58–1.13)	0.074
EGFR status (WT vs. MT)	0.68 (0.37–1.23)	0.204		
SII ($\geq 1,270$ vs. $< 1,270$)	1.97 (1.46–2.65)	< 0.001	1.98 (1.47–2.68)	< 0.001

Y, yes; N, no; AC, adenocarcinoma; CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor receptor; F, female; HR, hazard ratio; M, male; MT, mutated status; NLR, Neutrophil to lymphocyte ratio; WT, wild-type status; NSCLC, non-small cell lung cancer.

Table 3 Univariate and multivariable analysis of predictors of PFS in patients treated with first-line therapy for locally advanced or metastatic NSCLC

Evaluated variables	Univariate Cox regression		Multivariable Cox regression	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (≥ 70 vs. < 70 years)	1.08 (0.85–1.35)	0.568		
Gender (F vs. M)	0.82 (0.64–1.06)	0.131	1.03	0.854
ECOG-PS (≥ 2 vs. < 2)	1.18 (0.77–1.82)	0.451		
Smoke status (Y vs. N)	1.15 (0.85–1.56)	0.377		
Tumor stage (IV vs. III)	1.19 (0.93–1.53)	0.168	0.99	0.987
Histology (non-AC vs. AC)	1.00 (0.82–1.21)	0.983		
EGFR status (WT vs. MT)	0.52 (0.34–0.79)	0.002	0.54	0.006
SII ($\geq 1,270$ vs. $< 1,270$)	1.32 (1.05–1.67)	0.020	1.48	0.026

Y, yes; N, no; AC, adenocarcinoma; CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor receptor; F, female; HR, hazard ratio; M, male; MT, mutated status; NLR, neutrophil to lymphocyte ratio; WT, wild-type status; NSCLC, non-small cell lung cancer; PFS, progression free survival.

In the 3 groups, the median OS was 47.0 (95% CI, 13.0 to 53.9), 19.4 (95% CI, 5.3 to 23.8) and 9.7 (95% CI, 3.9 to 12.5) months, respectively ($P < 0.001$, *Figure 2A*).

In the same view, we realized a prognostic model based on the results of the multivariate analysis for PFS. Patients were stratified for PFS based on the presence of 0, 1 or 2 factors. The median PFS was 8.7 (95% CI, 3.0 to 3.9), 5.8 (95% CI, 3.0 to 3.9) and 3.3 (95% CI, 3.0 to 3.9) months, respectively ($P < 0.001$, *Figure 2B*).

Discussion

Inflammation plays a fundamental role in pathogenesis and tumor progression in patients with NSCLC (15,16). In this view, hematological markers of systemic inflammation should be investigated as predictive and prognostic factors of tumor response. Among them, neutrophils, platelets and lymphocytes seem to be the principal candidate for this role.

Previous studies investigated the prognostic role of NLR,

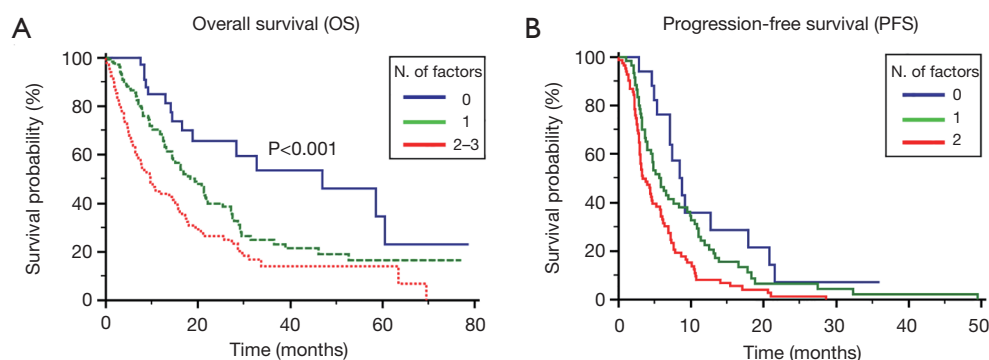


Figure 2 Prognostic models for OS (A) and PFS (B) in patients treated with first-line therapy for locally advanced or metastatic NSCLC. NSCLC, non-small cell lung cancer; PFS, progression free survival; OS, overall survival.

defined as the absolute neutrophil count divided by the absolute lymphocyte count (17-19). Other studies evaluated the platelet to lymphocyte ratio (PLR) (20), defined as the absolute platelets count divided by the absolute lymphocyte count, in NSCLC patients (21). High pretreatment NLR in patients treated with first-line platinum-based chemotherapy was demonstrated to be associated with shorter PFS and OS in advanced NSCLC patients (19). In the same view, high pretreatment PLR was associated to worse response to first-line chemotherapy and to poor prognosis in both non-metastatic and advanced NSCLC patients treated with chemotherapy (20,21).

The prognostic role of platelet count has been investigated in several studies. Recently, Inagaki *et al.* examined a series of 268 patients with advanced NSCLC and they reported that a platelet volume/platelet count (MPV/PC) ratio lower than 0.41 was associated with a worst prognosis (22). Similarly, the presence of preoperative thrombocytosis has been correlated with shorter OS and DFS in patients with resectable NSCLC (5), as well as with higher mortality and resistance to cisplatin-based chemotherapy in locally advanced and metastatic patients with lung cancer (23).

Recently, the negative prognostic role of high platelets/lymphocyte ratio (PLR) has been evaluated in this setting. Indeed, high PLR was associated with poor prognosis in patients with early-stage NSCLC treated with stereotactic radiation (24). In the same view, high PLR was a negative independent risk factor to first-line platinum-based chemotherapy in patients with advanced NSCLC (20).

Based on the recent results regarding the use of anti-programmed death-1 (PD-1)/PD-ligand 1 (PD-L1) agents nivolumab (25-27) and pembrolizumab (28,29), the research for reliable inflammatory biomarkers will

be a major focus in future years. Among them, the SII, a novel immune inflammation-based prognostic score that combines neutrophil, lymphocyte and platelet counts, seems to merit fully consideration. In fact, several studies demonstrated that other inflammatory indexes analyzing the same parameters, such as NLR and PLR, represents prognostic factors for patients receiving immunotherapy (30). In our study, we assessed the prognostic role of SII, a novel immune inflammation-based prognostic score that combines neutrophil, lymphocyte and platelet counts. We showed that a SII higher than 1,270 is associated with a shorter OS and PFS in patients with locally advanced or metastatic NSCLC treated with first-line chemo- or targeted therapies. Moreover, SII resulted a significant independent prognostic factor for both OS and PFS at univariate and multivariate analyses.

Based on these results, we designed two different prognostic models for OS and PFS. Regarding OS, a model based on the presence of ECOG-PS ≥ 2 , IV tumor stage and SII $>1,270$ has allowed identifying 3 different groups of prognostic risk. As for PFS, EGFR status and SII $>1,270$ permitted to stratify patients into good, intermediate and poor risk categories. The higher cut off-value in our study [1,270], compared to the cut off-value identified by Hu and his group [330] may be explained by the major frequency of thrombocytopenia in patients with cirrhosis and HCC (31).

However, there are some limitations to this study, due firstly to its retrospective nature, which is susceptible to bias in data selection and analysis. In addition, other inflammatory markers, including CRP (C reactive protein) or procalcitonin, are not routinely measured at our institutions. Furthermore, SII can be influenced by concurrent infection and drugs that cannot be accounted in this study.

Conclusions

In conclusion, SII seems to have a significant prognostic impact in patients with locally advanced or metastatic NSCLC. These observations should be considered relevant for the therapeutic strategy and management of such patients. Further studies in larger populations should be conducted to validate the prognostic role of SII and our risk models in clinical practice.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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. Our project has been approved by local Ethics Committee (ID 2019-146) and the work conforms to the provisions of in accordance with the Helsinki Declaration as revised in 2013.

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