Prognostic Role of Lung Immune Scores for Prediction of Survival in Limited-stage Small Cell Lung Cancer

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Abstract. *Background/Aim: Previous studies have suggested the prognostic value of the Lung Immune Prediction Index (LIPI) and the Gustave Roussy Score (GRIM) as prognostic markers in advanced small cell lung cancer (SCLC). However, LIPI and GRIM score have not been evaluated in patients with limited stage SCLC (LS-SCLC). Patients and Methods: Pretreatment LIPI and GRIM score of 33 (43%) patients out of 77 LS-SCLC patients treated with chemoradiotherapy (CRT) during 2004-2015 were included. Results: The median overall survival (OS) time in the good, intermediate, and poor LIPI subgroups were 14, 17 and 3 months (p=0.973) and 14, 17 and 17 months in the GRIM subgroups. In univariate analysis, patients age <65 years (p=0.008), concurrent chemotherapy (p=0.028), and administering prophylactic cranial irradiation (PCI) (p=0.031) were associated with improved OS. Using Cox regression analysis, age remained significant (HR=3.299, p=0.031) and PCI showed a trend (HR=2.801, p=0.06). Conclusion: Independent predictors of overall survival were identified and can contribute to improved treatment personalization. Concurrent chemotherapy and PCI after CRT were associated with improved OS compared to LIPI- and GRIM-score, which had no prognostic impact in LS-SCLC.*

Small cell lung cancer (SCLC) is a highly aggressive cancer subtype with a rapid doubling time, early metastases, and dismal prognosis. State-of-the-art treatment of limited-stage SCLC (LS-SCLC) patients compromises definitive chemoradiotherapy (CRT) followed by prophylactic cranial irradiation (PCI) (1-7). Particular attention should be paid to patients with severe comorbidities, reduced performance status, or advanced age, as intensive treatment is not tolerated (8). However, selected patients may need therapy intensification in order to improve local and distant control. Hence for patient-centered therapy decision-making, individual clinical parameters such as gender, age, performance status, and smoking habit must be considered (1). Systemic inflammation seems to be involved in tumor promotion and progression. Markers of systemic inflammation are associated with a poor outcome and can be used for risk stratification (9). Several novel and clinically-practical parameters have been introduced as independent prognostic factors, such as the Lung Immune Prognostic Index (LIPI), the Gustave Roussy Immune Score (GRIM-Score), the Neutrophil-Lymphocyte Ratio (NLR) and the derived Neutrophil-Lymphocyte Ratio (dNLR) (9-11). The prognostic role of the GRIM and LIPI scores in non-small cell lung cancer (NSCLC) regarding OS and progression-free survival (PFS) as well as their importance as predictive indicators of treatment response to immunotherapy with immune checkpoint inhibitors (ICIs) has already been validated (12, 13). However, to the best of our knowledge, there are no studies on the prognostic value of the GRIM- and LIPI-score in LS-SCLC patients yet. In the present study, we aimed to validate the prognostic value of the LIPI and GRIM scores in patients with LS-SCLC receiving platinum-based CRT.

Patients and Methods

Study population. The medical charts of 77 consecutive patients with LS-SCLC that were treated with curative-intent platinum-based chemoradiotherapy between 01/2004 and 12/2015 were assessed. After excluding patients with unknown blood parameters before

Table I. *Patient and treatment characteristics.*

	N (%)
Total	33 (100)
Age	
Median years	63
≥65 years	15 (45)
Gender	
Male	13 (39)
Female	20 (61)
T-stage	
1	4 (12)
2	9 (27)
3	8 (24)
4	12 (36)
N-category	
0	1 (3)
1	2 (6)
2	18 (55)
3	12 (36)
Karnofsky performance status	
80-100%	29 (88)
50-70%	4 (12)
Concurrent chemotherapy	
Yes	18 (55)
No	15 (46)
Radiation regimen	
Once daily	24 (73)
Twice daily	9 (27)
Prophylactic cranial irradiation	
Yes	24 (73)
No	9 (27)
NLR	
<3	23 (70)
≥3	10 (30)
dNLR	
<3	9 (27)
≥3	24 (73)
Gustave Roussy Immune Score	
Favorable prognostic group	19 (58)
Intermediate prognostic group	11 (33)
Poor prognostic group	3 (9)
The Lung Immune Prognostic Index	
Favorable prognostic group	21 (64)
Intermediate prognostic group	10 (30)
Poor prognostic group	2 (6)

NLR: Neutrophil-lymphocyte Ratio; dNLR: derived neutrophil-lymphocyte ratio.

initiation of radiotherapy, 33 (43%) patients remained and were included in the analysis. Patient and treatment characteristics are summarized in Table I. Patients received a median radiation dose in equivalent dose of 2Gy fractions (EQD2) of 59 (range:42-67) Gy or were treated with hyperfractionated accelerated radiotherapy (14). 55% of all patients were treated with concurrent platinum-based chemotherapy. PCI was administered after the end of thoracic irradiation in 73% of all patients. The Institutional Research Ethical Review Board approved the study (approval number: 17-230).

Assessment of immune scores based on blood cell counts. Blood parameters of all patients were assessed and included lymphocyte count, leucocyte count, neutrophil count, neutrophil-to-lymphocyte ratio (NLR), derived NLR (defined as neutrophils/(leucocytes-neutrophils) ratio), LDH and serum albumin levels. For our analysis, we chose the latest blood values before the initiation of radiotherapy (up to two weeks before treatment start). The calculation of the GRIM score is based on the neutrophil to leukocyte ratio (NLR) (>6), the lactate dehydrogenase (LDH)>upper limit of normal (ULN), and the serum albumin (ALB) concentration (<3.5) (15). The Lung Immune Prognostic Index (LIPI) includes the blood levels LDH>ULN and the derived NLR (dNLR: neutrophils/[leucocytes-neutrophils]), >3 of pretreated patients and stratifies patients into "poor," "intermediate," and "good" prognostic groups (16).

Statistical analysis. Statistical analyses were performed using SPSS statistics 25 (IBM, New York, USA) and R version 3.5.3. Subgroups were compared using the log-rank test. All significant variables in univariate analysis were included in a multivariate Cox regression analysis. The proportional hazard assumption of the Cox regression analysis was tested. Overall survival was defined as the time between the last day of radiotherapy and death. For all statistical analyses, a significance level of $\alpha=0.05$ was defined.

Results

Median survival time in our patient cohort was 17 months (range=2-44 months). 1- and 2-year-survival rates were 58% and 36%, respectively (Table II). Median survival in the good, intermediate, and poor LIPI subgroup was 14, 17 and 3 months ($p=0.973$). Median survival of the GRIM subgroups was 14, 17, and 17 months in the favorable, intermediate, and poor prognosis group ($p=0.984$). In univariate analysis, patients with an age of <65 years, patients treated with concurrent chemotherapy, and patients receiving PCI after chemoradiotherapy showed improved overall survival (median OS=11 *vs.* 36 months ($p=0.008$), 12 *vs.* 36 months ($p=0.028$) and 12 *vs.* 20 months ($p=0.031$) (Figure 1a-c). In multivariate analysis, age was found to be an independent prognostic factor (hazard ratio (HR)=3.299, 95% confidence interval (CI)=1.119-9.726, $p=0.031$), concurrent platinum-based chemotherapy (HR=1.101, 95%CI=0.328-3.702, $p=0.876$) and PCI after chemoradiotherapy (HR=2.801, 95%CI=0.956-8.197, $p=0.06$) were not.

Discussion

Our study aimed to validate the GRIM and LIPI score for patients with LS-SCLC undergoing CRT. The objective was driven by the fact that cancer immunology has recently gained increasing importance in the treatment of SCLC. Although a combination therapy of platinum-etoposide chemotherapy and thoracic radiotherapy has remained the first-line treatment for LS-SCLC for more than 20 years, ICIs have been approved for certain indications in SCLC, especially extensive or recurrent SCLC (14). The CASPIAN trial found that first-line therapy

Table II. *Univariate and multivariate analysis of overall survival based on clinicopathological characteristics.*

	12 months survival rate (%)	24 months survival rate (%)	*p*-value (univariate analysis)	*p*-value (multivariate analysis)
Age				
<65 years	72	56		
≥65 years	40	13	0.008	0.031
Gender				
Male	46	31		
Female	65	40	0.302	
T-stage				
1-2	50	25		
3-4	59	38	0.358	
N-category				
0-1	67	0		
2-3	57	40	0.296	
Karnofsky performance status				
80-100%	62	38		
50-70%	25	25	0.246	
Concurrent chemotherapy				
Yes	67	56		
No	47	13	0.028	0.876
Radiation regimen				
Once daily	54	29		
Twice daily	67	56	0.246	
Prophylactic cranial irradiation				
Yes	63	46		
No	44	11	0.031	0.060
NLR				
<3	65	35		
≥3	40	40	0.634	
dNLR				
<3	63	33		
≥3	44	33	0.725	
Gustave Roussy Immune Score				
Favorable prognostic group	58	37		
Intermediate prognostic group	55	36		
Poor prognostic group	67	33	0.984	
The Lung Immune Prognostic Index				
Favorable prognostic group	52	33		
Intermediate prognostic group	70	40		
Poor prognostic group	50	50	0.973	

p-value of univariate analysis was calculated by log-rank test; *p*-value of significant variables in univariate analysis was calculated by multivariate Cox regression analysis. NLR: Neutrophil-lymphocyte ratio; dNLR: derived neutrophil-lymphocyte ratio.

with durvalumab plus platinum-etoposide chemotherapy improved OS in extensive stage SCLC compared to standard chemotherapy (18). The CheckMate 032 phase I/II trial has shown that nivolumab monotherapy is an effective option for third-line therapy of recurrent SCLC (19). Patients with recurrent or metastatic SCLC who had undergone at least two previous therapy lines could further benefit from pembrolizumab regardless of PD-L1 expression (20). Implementation of ICIs in LS-SCLC is currently under investigation (30, 31). A randomized Phase II/III clinical trial (NCT03811002/NRG-LU005) evaluates the standard treatment compared to chemoradiotherapy plus atezolizumab (30). In

addition, a randomized controlled multicenter study (NCT03703297/ADRIATIC) currently investigates consolidation treatment with durvalumab or durvalumab in combination with tremelimumab in LS-SCLC patients without disease progression after CRT (31). In this context, prognostic prediction tools such as the NLR, LIPI, and GRIM score could be helpful in order to tailor treatment individualization and predict outcome. The GRIM score was initially developed to select suitable patients for phase I trials of ICIs, and the LIPI score is designed to predict response to immunotherapy, guide treatment selection, and identify those patients who are unlikely to benefit from ICIs (13, 15, 16). In ED-SCLC, the GRIM-score can serve as a
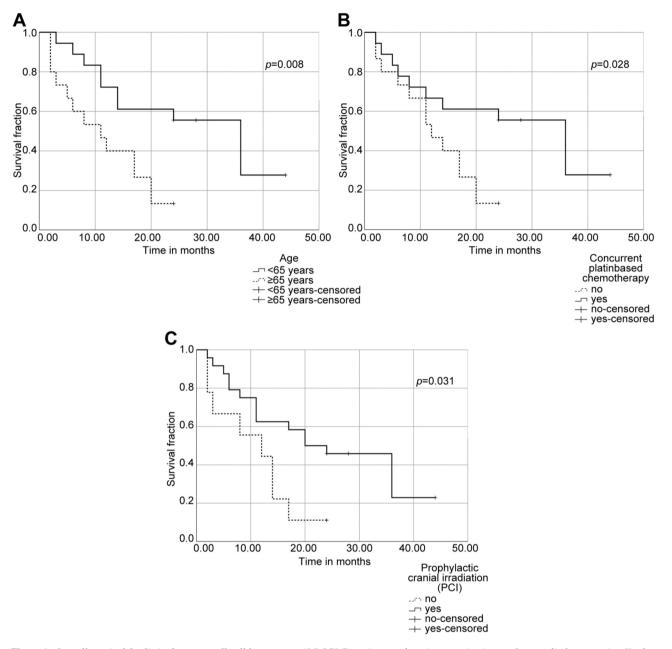
Figure 1. *Overall survival for limited-stage small cell lung cancer (LS-SCLC) patients undergoing curative-intent chemoradiotherapy using Kaplan-Meier analysis and log-rank test. (A) Kaplan-Meier survival curve for overall survival according to age groups. (B) Kaplan-Meier survival curve for overall survival regarding concurrent platinum-based chemotherapy. (C) Kaplan-Meier survival curve for overall survival (OS) regarding prophylactic cranial irradiation (PCI).*

reliable prognostic factor of OS (10). In non-small cell lung cancer (NSCLC), the prognostic impact of the GRIM-Score has also been investigated in earlier stages (operable stage I and II NSCLC) (21). Nakaya *et al.* report that the NLR during treatment of advanced NSCLC with nivolumab could be a predictive marker of treatment response or PFS. However, no pre-treatment marker could be identified (24). Another study

conducted by Suh *et al.* reported that a high NLR (≥5) at six weeks after treatment with anti-PD-1 antibody is associated with inferior PFS in patients with advanced NSCLC (25). An Italian study with two centers including 120 patients with SCLC and large cell neuroendocrine carcinoma (LCNEC) showed that the LIPI score allowed for patient stratification into good (15 months), intermediate (11 months) and poor (9

months) groups according to their median OS (23). The baseline of both scores is the NLR, which reflects the inflammatory balance and can serve as a prognostic biomarker of OS and PFS. Our study found no prognostic relevance of the GRIM- and LIPI-Score for LS-SCLC. Instead, our study supports the treatment with concurrent platinum-based chemotherapy and PCI after CRT. Moreover, we found that age is an independent prognostic factor in the treatment of LS-SCLC, thereby emphasizing the importance of patient-centered therapy assessment. Age should be considered together with gender, Karnofsky performance score, tumor stage, hemoglobin level, and comorbidity scale in order to improve treatment individualization and shared-decision making (26-28).

Several limitations need to be considered such as the retrospective design and small sample size which may have led to selection bias and therefore need to be critically considered. Moreover, not all patients of the recruitment period could be included due to unknown pretreatment blood parameters. Consequently, alternative conclusions could be found in larger retrospective or randomized prospective studies. Despite these limitations, this is the first study to provide an initial assessment of the prognostic relevance of LIPI and GRIM scores in LS-SCLC. Although the GRIM and LIPI scores in our study showed no prognostic impact on the treatment of LS-SCLC, our data are consistent with recent studies. Concurrent platinum-based chemotherapy and administering PCI after CRT are associated with improved survival, and patient age is an independent prognostic factor of high clinical relevance for risk stratification.

Conclusion

Age is an independent prognostic factor in the treatment of LS-SCLC and should be critically considered in treatment allocation. Administration of concurrent chemotherapy and PCI after the end of CRT were associated with improved OS compared to pretreatment LIPI- and GRIM-score which had no significant impact. The results of ongoing trials investigating immune checkpoint inhibition in LS-SCLC are eagerly awaited. Pretreatment LIPI- and GRIM-score may serve as prognostic biomarkers in these studies and should be evaluated in multimodal treatment including immune checkpoint inhibition for LS-SCLC.

Conflicts of Interest

The Authors declare that there is no conflict of interest.

Authors' Contributions

LS, LK and RA were involved in the conceptualization of the project, data collection and text drafting. JT, RA, CE and FM critically reviewed and edited the text. LK and RA visualized the data and performed the statistical analysis. FM and LK had the supervision.

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