Significance of Glasgow prognostic scores in NSCLC patients treated with immunotherapy after platinum-based cytotoxic chemotherapy

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Research Article

Keywords: Immunotherapy, albumin, C-reactive protein, non-small cell lung cancer, mutations

Posted Date: February 19th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-191781/v1

Version of Record: A version of this preprint was published at In Vivo on January 1st, 2021. See the published version at https://doi.org/10.21873/invivo.12642.

Abstract

Background: The Glasgow prognostic score (GPS) reflects the host's systemic inflammatory response and is a validated prognostic factor in lung cancer. However, little is known about the prognostic role in non-small cell lung cancer (NSCLC) patients treated with immunotherapy after platinum-based cytotoxic chemotherapy.

Methods: This study used a lung cancer cohort of the Catholic Medical Center of Korea between January 2018 and September 2020. We included patients who were diagnosed with unresectable advanced stage NSCLC or recurrent disease after pulmonary resection and had received at least one regimen of platinum-based chemotherapy before the administration of immunotherapy. The prognostic value of the GPS was assessed in patients with NSCLC treated with anti-PD1 or anti-PD-L1 (pembrolizumab, nivolumab, or atezolizumab). The GPS was calculated using C-reactive protein and albumin concentrations within one week before starting anti-PD1 or anti-PD-L1 treatment.

Results: A total of 78 patients with NSCLC treated with immunotherapy as second or further-line therapy after platinum-based chemotherapy were included in the study. Kaplan-Meier analysis revealed that higher GPS values were significant predictors of shorter immune-related progression-free survival (irPFS) (log-rank $P < 0.001$) and overall survival (OS) (log-rank $P < 0.001$). In the Cox regression multivariate analysis, the hazard ratios for irPFS were 0.249 (95% confidence interval [CI]: 0.084 – 0.739, $P = 0.012$) for PD-L1 expression ≥ 50% and 9.73 (95% CI: 2.931 – 32.298, $P < 0.001$) for a GPS of 2 relative to a GPS of 0. Older age ($P = 0.033$), lower PD-L1 expression ($P = 0.036$), and higher GPS values ($P = 0.007$) were independently associated with shorter OS.

Conclusions: Higher GPS values were identified as a poor prognostic factor for OS and irPFS in NSCLC patients who received immunotherapy as second or further-line therapy after platinum-based chemotherapy.

Background

The introduction of immune-checkpoint inhibitors (ICIs) into the therapy for non-small cell lung cancer (NSCLC) has transformed the therapeutic landscape of metastatic NSCLC [1]. The expression of programmed death-ligand 1(PD-L1) on tumor cells and tumor mutation burden (TMB) have been used in qualification of patients to ICIs but not all patients with these predictive factors benefit from ICIs [2]. However, the proper predictive factors for using ICIs to treat NSCLC patients have not been developed.

Inflammation is an important factor in tumor progression and is associated with poor response to treatment. The response to cancer treatment depends not only on the tumor's characteristics and tumor stage but also patient-related factors including nutrition and inflammation status [3]. Recently, systemic inflammatory response to predict progression and survival has been reported patients with malignancies. Thus, cancer-related prognosis has been validated using inflammatory markers such as the neutrophil-

lymphocyte ratio (NLR) or lung immune prognostic index consisting of the NLR and lactate dehydrogenase (LDH) levels, and the systemic inflammation response index [2, 4].

The Glasgow prognostic score (GPS), reflecting the host systemic inflammatory response and immune status has been validated as a prognostic factor in many malignancies. The GPS is the combination of the C-reactive protein (CRP) concentration (> 10 mg/L) and hypoalbuminemia (< 35 g/L) [5, 6]. The association of the GPS and ICIs in lung cancer patients has been explored. However, previous studies had small sample sizes or evaluated the post-treatment GPS in lung cancer patients treated with ICIs.

Few previous studies have evaluated the prognostic value of the GPS in metastatic NSCLC patients treated with ICIs who received at least one regimen of cytotoxic chemotherapy before the administration of ICIs. In this study, we retrospectively analyzed the survival and immune-related progression-free survival (irPFS) data of patients with metastatic NSCLC and explored the prognostic role of the GPS in these patients.

Methods

We used the database of the Catholic Medical Center lung cancer registry. Since October 2014, seven hospitals of the Catholic University of Korea (Seoul St. Mary's Hospital, Yeouido St. Mary's Hospital, Eunpyeong St. Mary's Hospital, Uijeongbu St. Mary's Hospital, Bucheon St. Mary's Hospital, Incheon St. Mary's Hospital, and St. Vincent's Hospital) have consecutively enrolled lung cancer patients. Clinical information including stage, pathology, treatment modality, and survival was systematically recorded by qualified managers to improve the accuracy of the data. The researchers were permitted to access by newly assigning serial numbers and anonymizing the dataset.

Patients were eligible for the study if they were diagnosed from January 2018 to March 2020 with histologically confirmed NSCLC and received ICIs as second-line or further-line therapy after treatment failure with platinum-based cytotoxic chemotherapy. Patients who received ICIs as first-line therapy, were diagnosed with small cell lung cancer, received post-chemoradiation consolidation treatment with durvalumab, were lost to follow up, or had no pre-treatment CRP and albumin levels were excluded. The study flow is summarized in Fig. 1. The follow-up period ended on September 30, 2020.

Data

We extracted the following data from the patient medical records: patient demographics, smoking history, stage of lung cancer, Eastern Cooperative Oncology Group performance status, laboratory data, history of chemotherapy and/or radiation, survival status, and the dates of disease progression and death. Blood samples drawn within one week before ICI treatment were used to compile a pretreatment GPS for each patient using the laboratory values. The patients were classified into three groups based on GPS values as follows: (I) GPS of 2, elevated CRP level (> 1.0 mg/dL) and hypoalbuminemia (< 3.5 g/dL); (II) GPS of 1, elevated CRP level or hypoalbuminemia; and (III) GPS of 0, neither elevated CRP level nor

hypoalbuminemia [5, 7]. The serum CRP levels were measured using immunoturbidimetric assays (CRPL3, Roche Diagnostics, Indianapolis, IN, USA).

Statistical analysis

The patient baseline demographics and clinical outcomes were compared according to the GPS. We used Pearson's chi-squared test to compare the discrete variables and the Student's t-test or analysis of variance to compare the continuous variables. The Mann-Whitney test was used to compare the median values. Hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs) were calculated for the predictors that were significant in multivariate Cox regression analysis. A two-sided P value of < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS for Windows software (ver. 20.0; IBM Corp., Armonk, NY, USA)[8] .

Results

Patient characteristics

Overall, 122 NSCLC patients treated with ICIs were enrolled, of whom 44 met the exclusion criteria (treatment with ICIs as first-line therapy, small cell lung cancer treated with ICIs, treatment with durvalumab, and patients lost to follow-up, or those who had no pre-treatment CRP/albumin levels). Thus, 78 patients were finally included in our analysis (Fig. 1). The mean age of the included subjects was 67.1 ± 9.17 years (range, 38.0–84.0 years). There were 64 (82.1%) males. Of all the included patients, 19 (24.4%), 35 (44.9%), and 24 (30.8%) were classified into the GPS 0, GPS 1, and GPS 2 groups, respectively. We compared these three groups and explored the clinical factors predicting treatment outcomes including overall survival (OS) and irPFS. The total and median follow-up times were 12.7, 14.2, 15.0, and 6.4 person-months, respectively.

The baseline characteristics of these three groups are summarized in Table 1. The mean age and smoking history were not different between the three groups. The proportion of poor performance status, histologic type, treatment line of ICIs, driving mutations, and PD-L1 expression were similar between the three groups. However, the GPS 0 group tended to receive atezolizumab and the GPS 2 group tended to receive pembrolizumab as ICIs ($P = 0.042$).

Table 1
Baseline characteristics of NSCLC patients treated with immunotherapy according to GPS values

Variables	GPS = 0 (n = 19)	GPS = 1 (n = 35)	GPS = 2 (n = 24)	P-value
Age	66.74 ± 9.26	66.77 ± 9.04	66.88 ± 9.77	0.999
Sex, male	14 (73.7)	28 (80.0)	22 (91.7)	0.285
Smoking history				0.753
Never-smoker	3 (15.8)	6 (31.6)	10 (52.6)	
Ever-smoker	3 (8.6)	14 (40.0)	18 (51.4)	
Current-smoker	1 (4.2)	10 (41.7)	13(54.2)	
Pack-years	49.75 ± 24.59	36.29 ± 19.73	40.72 ± 17.31	0.102
Performance status ≥ 2	10 (41.7)	11 (45.8)	2 (8.3)	0.300
Histologic type				0.773
Adenocarcinoma	8 (42.1)	18 (51.4)	14 (58.3)	
Squamous cell carcinoma	10 (52.6)	15 (42.9)	10 (41.7)	
Others	1 (5.3)	2 (5.7)	0(0.0)	
Treatment line				0.121
2nd	15 (78.9)	32 (91.4)	20 (83.3)	
≥ 3rd	4 (21.0)	3 (8.6)	4 (16.7)	
ICIs				0.042
Pembrolizumab	9 (47.4%)	20 (57.1%)	11 (45.8%)	
Nivolumab	1 (5.3%)	6 (17.1%)	9 (37.5%)	
Atezolizumab	9 (47.4%)	9 (25.7%)	4 (16.7%)	
EGFR mutation, positive	0 (0.0)	2 (5.9)	1 (4.2)	0.791
ALK rearrangement, positive	0 (0.0)	0 (0.0)	0 (0.0)	
PD-L1 expression				0.508
0%	4 (21.1)	3 (8.6)	3 (12.5)	

Data are presented as the mean ± standard deviation (range) or number (%).

GPS, Glasgow prognostic score; NSCLC, non-small cell lung cancer; ICI, immune check-point inhibitor; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma receptor tyrosine kinase; PD-L1, programmed death-ligand 1

Variables	GPS = 0 (n = 19)	GPS = 1 (n = 35)	GPS = 2 (n = 24)	P-value
1–10%	4 (21.1)	8 (22.8)	4 (16.7)	
11–49%	3 (15.8)	3 (8.6)	5 (20.8)	
≥50%	6 (31.6)	21 (60.0)	12 (50.0)	
Data are presented as the mean ± standard deviation (range) or number (%).				
GPS, Glasgow prognostic score; NSCLC, non-small cell lung cancer; ICI, immune check-point inhibitor; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma receptor tyrosine kinase; PD-L1, programmed death-ligand 1				

Prognostic Analysis

The GPS 2 group displayed a shorter median irPFS than the GPS 0 or GPS 1 groups [23.0 (95% CI: 12.43–33.57) days vs. 89.0 (95% CI: 57.6–120.4) days vs. 107.0 (95% CI: 41.92–172.1) days, P < 0.001]. Also, the GPS 2 group showed significantly shorter median OS than the GPS 0 or GPS 1 groups [412.9 (95% CI: 278.5–547.27) days vs. 593.7 (95% CI: 504.3–683.2) days vs. 768.5 (95% CI: 655.7–881.2) days, P < 0.001] (Fig, 2A and B).

In the multivariate analysis of irPFS, the HR was 0.249 (95% CI: 0.084–0.739, *P* = 0.012) for PD-L1 expression ≥ 50% and 9.73 (95% CI: 2.931–32.298, *P* < 0.001) for GPS 2 (Table 2). In the multivariate analysis for OS, the HR was 0.189 for PD-L1 expression between 1 and 10%, 0.297 for PD-L1 expression ≥ 50%, 4.247 in the GPS 1 group, and 9.710 in the GPS 2 group (Table 3).

Table 2
Univariate and multivariate analysis for predicting progression-free survival in NSCLC patients treated with immunotherapy after platinum-based cytotoxic chemotherapy

	Univariate analysis			Multivariate analysis		
Variables	HR	95% CI	P-value	HR	95% CI	P-value
Age	0.988	0.956–1.021	0.480			
Sex, male	1.637	0.802–3.341	0.176			
Smoking status			0.255			
Ex-smoker	2.204	0.812–5.985	0.121			
Current smoker	1.578	0.586–4.248	0.367			
Pack-years	1.004	0.991–1.017	0.550			
Stage	1.774	0.973–3.235	0.061	1.083	0.530–2.211	0.827
Histological cell type						
Adenocarcinoma						
Squamous cell carcinoma	1.261	0.293–5.422	0.755			
adenosquamous cell carcinoma	0.82	0.189–3.553	0.791			
NOS	0.403	0.036–4.534	0.462			
PD-L1			0.014			0.015
0%						
1–10%	1.082	0.369–3.169	0.886	0.38	0.109–1.329	0.130
11–49%	1.619	0.569–4.608	0.367	1.124	0.357–3.545	0.842
≥ 50%	0.436	0.170–1.119	0.084	0.249	0.084–0.739	0.012
GPS			< 0.001			< 0.001
0						
1	1.051	0.479–2.305	0.902	2.146	0.814–5.656	0.123
2	5.011	2.061–12.187	< 0.001	9.73	2.931–32.298	< 0.001

NSCLC, non-small cell lung cancer; HR, hazard ratio; CI, confidence interval; NOS, not otherwise specified; PD-L1, programmed death-ligand 1; GPS, Glasgow prognostic score

Table 3
Univariate and multivariate analysis for predicting overall survival in NSCLC patients treated with immunotherapy after platinum-based cytotoxic chemotherapy

	Univariate analysis			Multivariate analysis		
variable	HR	95% CI	P-value	HR	95% CI	P-value
Age	1.060	1.016–1.107	0.007	1.067	1.005–1.133	0.033
Sex, male	2.652	0.934–7.531	0.067	1.305	0.282–6.032	0.733
Smoking status			0.175			
Ex-smoker	3.633	0.842–15.683	0.084			
Current smoker	2.530	0.575–11.133	0.220			
Pack-years	1.014	0.998–1.029	0.085	1.015	0.998–1.033	0.083
Stage	1.492	0.757–2.942	0.248			
Histologic cell type			0.388			
Adenocarcinoma						
Squamous cell carcinoma	1.005	0.515–1.959	0.989			
adenosquamous cell carcinoma						
NOS	3.618	0.822–15.919	0.089			
PD-L1			0.007			0.036
0%						
1–10%	0.550	0.145–2.081	0.379	0.263	0.053–1.294	0.100
11–49%	3.290	0.957–11.309	0.059	1.455	0.361–5.874	0.598
≥ 50%	0.776	0.261–2.309	0.649	0.364	0.094–1.410	0.144
GPS			0.002			0.007
0						
1	3.513	1.028–12.007	0.045	4.498	1.164–17.388	0.029

NSCLC, non-small cell lung cancer; HR, hazard ratio; CI, confidence interval; NOS, not otherwise specified; PD-L1, programmed death-ligand 1; GPS, Glasgow prognostic score

	Univariate analysis			Multivariate analysis		
2	8.459	2.402–29.793	0.001	8.574	2.218–33.140	0.002

NSCLC, non-small cell lung cancer; HR, hazard ratio; CI, confidence interval; NOS, not otherwise specified; PD-L1, programmed death-ligand 1; GPS, Glasgow prognostic score

Discussion

In the present study, we compared the clinical outcomes of NSCLC patients treated with ICIs as second-line or further-line therapy after treatment failure with platinum-based cytotoxic chemotherapy according to the GPS values and explored the prognostic role of GPS values for treatment outcomes. We found that the baseline characteristics were not different according to GPS. Patients with higher GPS values displayed shorter median irPFS and OS than those in the GPS 0 or GPS 1 groups. In multivariate analysis, higher PD-L1 expression was negatively associated and higher GPS was positively associated with shorter irPFS and OS.

Chronic inflammation is known to be associated with tumor development through the induction of oncogenic mutations, genomic instability, early tumor promotion, and enhanced angiogenesis [9]. Various cancers induce an inflammatory microenvironment [10]. Nutrition is a critical component of immune responses [11]. In lung cancer, systemic inflammation, malnutrition, and tumor immune microenvironments are associated with each other, and these are key determinants of tumor progression and treatment response [3]. Elevated levels of circulating CRP could be a marker of the increased predisposition to malignancy due to chronic inflammation, a marker of occult cancer leading to inflammation, or both [10].

In the era of immunotherapy in cancer treatment, proper predictive factors of NSCLC patients for immunotherapy have not been developed. The expression of PD-L1 on tumor cells and the TMB have been used in qualifying patients to receive immunotherapy, but not all patients with these predictive factors benefit from immunotherapy [2]. Patients with high TMB who received nivolumab and ipilimumab did not show significant survival benefit compared to those who received chemotherapy [12]. The presence of immune cells in the anti-tumor immune response such as cluster of differentiation (CD)8-positive cytotoxic T lymphocytes as well as CD4-positive memory and regulatory T lymphocytes has been postulated as a prognostic marker of the disease course and predictors of activity or modulation of immune system function [13]. For simpler analysis, systemic inflammatory marker such as lung immune prognostic index which could be performed in clinical practice are suggested as biomarker for ICIs in lung cancer. Poor lung immune prognostic index combining the derived NLR and the LDH value is associated with poorer outcomes in patients treated with ICIs [14].

Several studies demonstrated that systemic inflammatory biomarkers in peripheral blood were predictive markers for treatment outcomes in different solid tumors including prostate, colorectal, and esophageal cancer, melanoma, and NSCLC [15–19]. Although the exact biological basis for these findings has not been thoroughly elucidated, inflammatory cells such as neutrophils play a significant role in tumor development and progression via effects on tumor cells or other components of the tumor microenvironment by secreting chemokines and cytokines such as transforming growth factor-ß, interleukin-6 (IL-6), and matrix metalloproteinase [20, 21]. CRP is a surrogate marker of IL-6, which is involved in the activation of immune cells, tumor migration and invasion, and epithelial-to-mesenchymal transition [22, 23].

Cancer prognosis is associated with not only tumor staging but also patient-related factors such as nutritional and functional decline. CRP represents systemic inflammation, and albumin reflects both systemic inflammation and the amount of lean tissue [24, 25]. GPS is a reliable independent prognostic factor in patients with various malignancies and also a marker for predicting prognosis, even in surgery, chemoradiation, and various subgroups incapable of surgery [5, 6]. In 15 studies including > 2,000 patients, GPS was associated with increased weight loss, poor performance status, increased comorbidity, increased proinflammatory and angiogenic cytokines, and complications from cancer treatments [5].

Few previous studies on the association between GPS and clinical outcomes in lung cancer patients treated with ICIs have been conducted. Taichi et al. reported that pretreatment modified GPS values were associated with shorter OS in NSCLC patients treated with atezolizumab [26]. In another study, post-treatment GPS predicted anti-PD1 treatment (nivolumab or pembrolizumab) efficacy in NSCLC patients [27]. These studies had small sample sizes from single institutions and reported the results of groups treated with anti-programmed cell death protein 1 (PD1) or anti-PD-L1 antibody. Our study had a large sample size and analyzed the prognostic role of pre-treatment GPS values in all of the NSCLC patients treated with anti-PD1 or anti-PD-L1 antibodies.

Limitations

This study had some limitations. First, it was a retrospective study. Nonetheless, our study was based on a lung cancer cohort with a moderate sample size using medical records that were faithfully collected from the time of enrollment, and the data were rechecked by authorized data managers. Therefore, data including the baseline characteristics and clinical outcomes were highly qualified and reliable. Also, we enrolled lung cancer patients from seven teaching hospitals in the Republic of Korea, so our data represent the Korean general population to some extent. Second, since our analyzed results were based on clinical parameters, we could not exactly elucidate the mechanisms of GPS on NSCLC patients treated with immunotherapy. However, hematologic biomarkers are promising predictors of the response to ICIs due to their convenience and accessibility in clinical practice.

Conclusions

The pre-treatment serum GPS is a promising value to identify NSCLC patients who could benefit more from ICIs as second-line or further-line therapy after treatment failure with platinum-based cytotoxic chemotherapy. Further large-scale studies are warranted to validate its clinical value.

List of abbreviations

ICIs, immune-checkpoint inhibitors; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1; TMB, tumor mutation burden; NLR, neutrophil-lymphocyte ratio; LDH, lactate dehydrogenase; GPS, Glasgow prognostic score; CRP, C-reactive protein; irPFS, immune-related progression-free survival; HRs, hazard ratios; CIs, confidence intervals; OS, overall survival; CD, cluster of differentiation; IL-6, interleukin-6; PD1, programmed cell death protein 1

List Of Abbreviations

ICIs, immune-checkpoint inhibitors; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1; TMB, tumor mutation burden; NLR, neutrophil-lymphocyte ratio; LDH, lactate dehydrogenase; GPS, Glasgow prognostic score; CRP, C-reactive protein; irPFS, immune-related progression-free survival; HRs, hazard ratios; CIs, confidence intervals; OS, overall survival; CD, cluster of differentiation; IL-6, interleukin-6; PD1, programmed cell death protein 1

Declarations

Ethics approval and consent to participate

This study was approved by the Clinical Research Ethics Committee of the Catholic Medical Center (approval number: XC20RIDI0192). All methods were performed in accordance with the Declaration of Helsinki, participants were informed about the study, the handling of personal data and how confidentiality would be maintained in the management of material and in publishing and presenting results. Researchers were permitted by the Clinical Research Ethics Committee of the Catholic Medical Center to conduct this study by accessing dataset newly assigned with a serial number whose personal information was removed after Ethics approval. We included only patients over 19 years old and written informed consent has been obtained from all patients prior to registry enrollment.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study have been kept confidential and are not available publicly because the Catholic Medical Center does not allow researchers to provide data personally or share publicly. but are available from the corresponding author upon reasonable request.

Competing interests

The authors have no conflicts of interest to declare.

Funding

None

Authors' contributions

HSK, CDY, and SKK contributed to protocol development, data analysis, and drafted the manuscript. AYS and JSK contributed to study conception and participated in its coordination. CKP, JWK, and SJK contributed to data checking and information retrieval. HSK, AYS, CDY, SHL, and JWK designed the study and contributed to the overall management of the study. All authors reviewed the manuscript and approved the final version of the manuscript.

Acknowledgements

The authors acknowledge and thank all research participants who supported and facilitated this research. We are also thankful to Bora Kwon, data manager for help with data collection and management of lung cancer registry.

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Figures

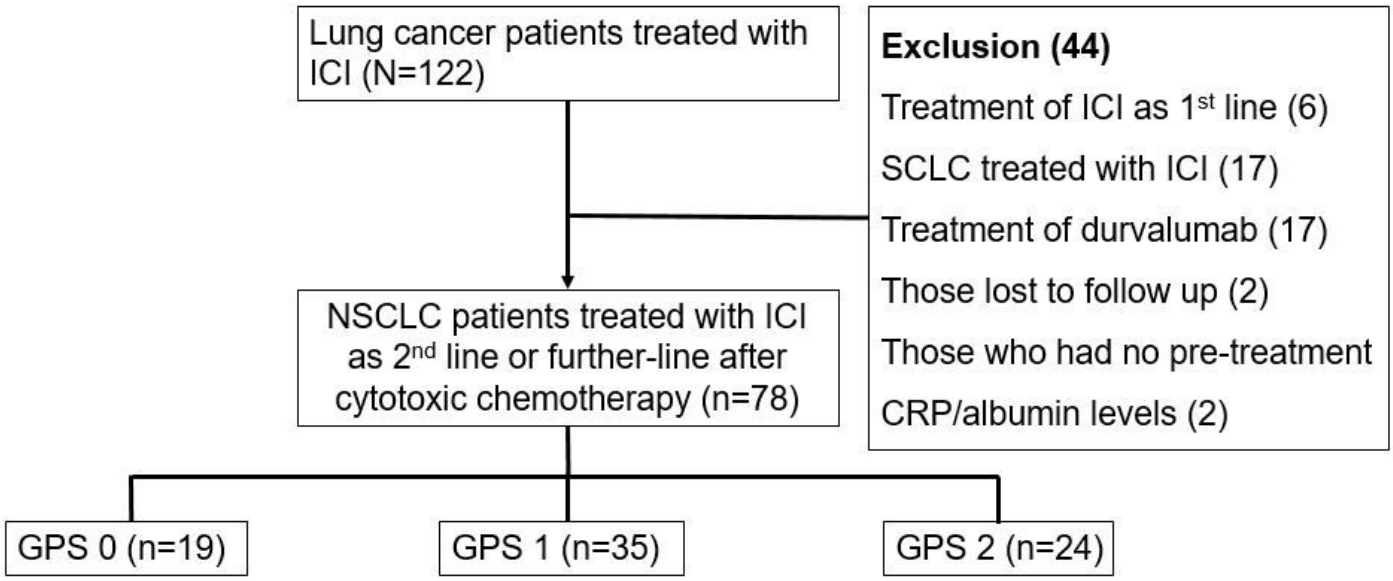

Figure 1

Study flow. ICI, immune-checkpoint inhibitors; SCLC, small cell lung cancer; CRP, C-reactive protein; NSCLC, non-small cell lung cancer, GPS, Glasgow prognostic score

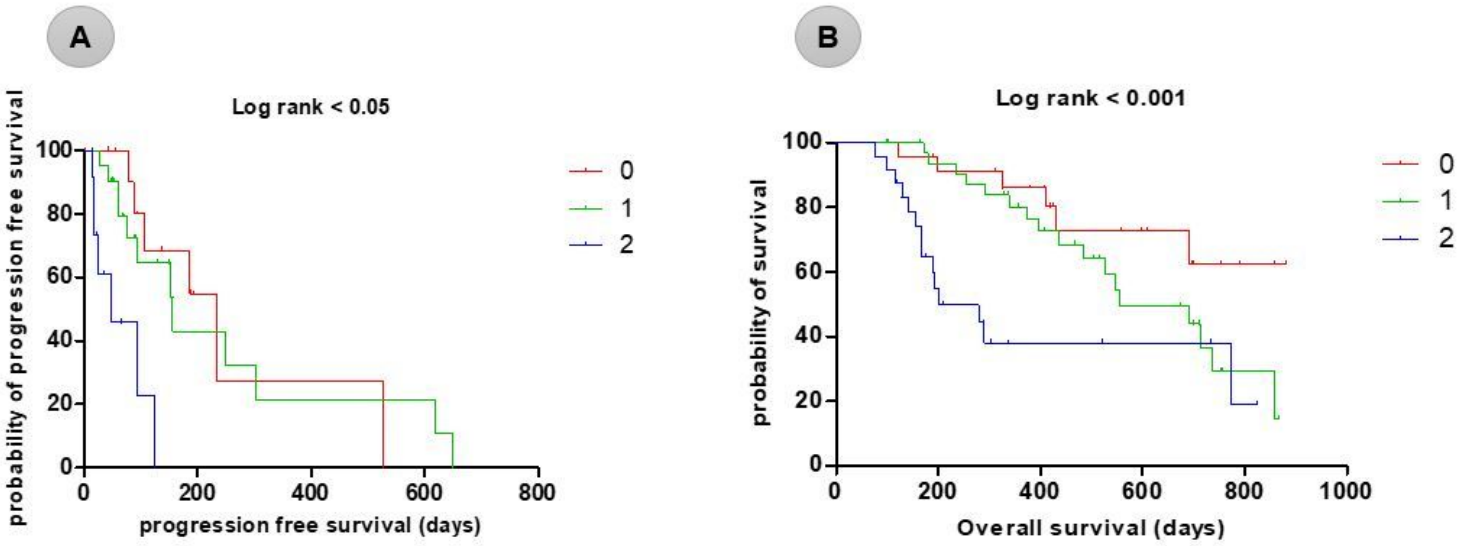

Figure 2

Clinical outcomes according to GPS in NSCLC patients treated with immunotherapy after platinum-based cytotoxic chemotherapy. GPS, Glasgow prognostic score; NSCLC, non-small cell lung cancer