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Original Article

High glasgow prognostic score associates with a poor survival in Chinese advanced non-small cell lung cancer patients treated with platinum-based first-line chemotherapy

Keju Su[1*], Xu Wang[1*], Lumei Chi[2], Yang Liu[3], Lina Jin[4], Wei Li[1]

[1]Cancer Center, First Affiliated Hospital, Jilin University, Changchun 130021, Jilin, China; [2]Second Department of Neurology, China-Japan Union Hospital of Jilin University, Changchun 130031, Jilin, China; [3]Department of Radiology, First Affiliated Hospital, Jilin University, Changchun 130021, Jilin, China; [4]School of Public Health, Jilin University, Changchun 130021, Jilin, China. [*]Equal contributors.

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Abstract: Aim: Glasgow prognostic score (GPS) has been used to predict the prognosis of non-small cell lung cancer (NSCLC) patients; however, limited data is available on advanced NSCLC patients of China. In this study, our aim was to evaluate the prognostic role of GPS in advanced NSCLC patients of China, receiving platinum-based first-line chemotherapy. Methods: Two hundred and seven advanced NSCLC patients of Chinese origin were prospectively and consecutively hospitalized between March 2011 and September 2014. They received platinum-based first-line chemotherapy. The main outcome measures included overall survival (OS) and progression-free survival (PFS). Results: The duration of median follow-up was 14.0 mo (range, 3.4-49.5 mo). The median OS of patients with GPS 2, 1, and 0 was 14.3 mo (8.5-20.2 mo), 15.9 mo (13.6-18.2 mo) and 19.1 mo (16.6-21.6 mo), respectively. The median PFS of patients with GPS 2, 1 and 0 was 8.3 mo (6.9-9.7 mo), 8.9 mo (8.0-9.7 mo) and 10.5 mo (8.8-12.1 mo), respectively. The results of univariate analysis indicated that GPS 2 is associated with a significantly shorter PFS (P=0.015) but not OS (P>0.05), while the results of multivariate analysis indicated that GPS 2 is associated with significantly shorter OS (P=0.049) and PFS (P=0.021). Conclusions: GPS 2 is an independent prognostic factor for poor OS and PFS in advanced NSCLC patients of China; these patients received platinum-based first-line chemotherapy.

Keywords: Non-small cell lung cancer, glasgow prognostic score, prognosis, overall survival, progression-free survival

Introduction

Lung cancer is the most common cause of cancer-associated death worldwide, because 1.18 million people die of lung cancer every year [1]. Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, with 85% of all lung cancer cases being those of NSCLC [2]. Although molecular targeted therapy is a newly-emerging treatment modality that may prolong survival period of NSCLC patients', very few patients have access to this advanced mode of treatment [3-5]. In conventional terms, a double-agent chemotherapy regimen, which is platinum-based, has been accepted as the first-line pharmacotherapeutic modality for NSCLC. However, even after having received standard platinum-based chemotherapy, patients with NSCLC have poor chances of survival if their disease was diagnosed at an advanced stage [6].

Multiple clinicopathological variables, such as nutritional status, performance status, and systemic inflammatory response, have been found to significantly improve the chances of survival of patients with lung cancer. Glasgow prognostic score (GPS) is a system predicting the chances of survival of cancer patients. Forrest *et al.* first proposed GPS as a predictive system to determine survival chances of cancer patients [7]. This technique has also been successfully tested on NSCLC patients [8-12]. Tomita *et al.* [8] have reported that a higher GPS is associated with a poor prognosis of operable NSCLC patients. Forrest *et al.* [9, 10] have proved that GPS is an independent prognostic factor in patients with advanced stages of NSCLC.

Very few studies have elucidated the prognostic role of GPS in advanced NSCLC patients of China [11]. Moreover, previous studies are characterized by a probable bias in that a non-standardized second-line therapy was used on NSCLC patients. Such a therapy predominantly involved the use of epidermal growth factor receptor (EGFR) and tyrosine kinase inhibitors (TKI), a major confounding factor. The primary objective of this study was to evaluate the prognostic role of GPS in advanced NSCLC patients of China. In our study, we also investigated the use of other confounding factors, TKI.

Materials and methods

Patients

The study protocol was approved at the Institutional Review Board of Cancer Center, First Affiliated Hospital, Jilin University, Changchun, Jilin, China. The study protocol was in accordance with the latest version of *the Declaration of Helsinki*. Between March 2011 and September 2014, 207 NSCLC patients were prospectively hospitalized at the Cancer Medicine Center, Cancer Center, First Affiliated Hospital, Jilin University, Changchun, Jilin, China. The inclusion criteria of patients were as follows: patients had to be at least 18 years old; they had been diagnosed with primary NSCLC through pathological or cytological analysis; the NSCLC progression was confirmed to be of stage cIIIb or cIV [13] as the performance status was either 0 or 1 according to the Eastern Cooperative Oncology Group (ECOG); the patients were scheduled to receive 4-6 cycles of double-agent first-line chemotherapy, which was platinum-based. The exclusion criteria were as follows: patients had developed a metastatic lung cancer, so they had concomitant malignancies; the lung cancer was a resectable disease (stage cI, cII and cIIIa); the patients received TKI as the first-line therapy; they might have had a complicated, pre-existing active infection or a chronic inflammatory disorder. All the patients signed a written informed consent letter before participating in this study.

Adjuvant therapy and follow-up protocols

Standard 4-6 cycles of double-agent chemotherapy, which was platinum-based, was provided as the first-line pharmacotherapy to included patients [14]. Treatment responses of subjects were evaluated using *the Response Evaluation Criteria in Solid Tumors* [15]. A radical and palliative radiation therapy was administered to non-metastatic and symptomatic metastasis patients, respectively. A second-line chemotherapy or TKI was administered to patients in whom the progression of the disease was confirmed. At the outpatient department, all the patients were followed up by an independent research staff every three months within the first year after the last cycle of chemotherapy. Thereafter, these patients were followed up every 6 months at the outpatient department. The overall survival (OS) was defined as the time interval between the time of diagnosis and that of documented death associated with any cause. The progression-free survival (PFS) was defined as the time interval between the time of diagnosis and that of documented disease progression or death due to any cause.

GPS evaluation

Venous blood samples were collected from included patients after they were admitted at our hospital without treatment. Using these samples, we measured serum C-reactive protein (CRP) and albumin. Furthermore, GPS was determined by a previously reported procedure [16]: GPS was assigned as 2 when the elevated CRP was ≥10 mg/L, while the patient had also developed hypoalbuminemia (<35 g/L); GPS was assigned as 1 when the patient developed either elevated CRP or hypoalbuminemia; GPS was assigned as 0 when the patient had normal serum levels of CRP (<10 mg/L) and albumin (≥35 g/L).

Statistical analysis

The statistical software package SPSS version 19.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The Kaplan-Meier method was used to estimate OS and PFS, which were subsequently analyzed using the log-rank test. Cox multivariate analysis was coupled with the backward and forward stepwise method. Thus, we determined potential prognostic factors and selected covariates. Using the Cox model, the proportional hazards assumption was assessed. For this purpose, we plotted Schoenfeld residuals against time; the hazard rate (HR) was expressed in terms of 95% confidence

Table 1. Clinicopathologic characteristics of advanced NSCLC patients treated with platinum-based first-line chemotherapy (n=207)

Characteristics	GPS 0 (n=49)	GPS 1 (n=111)	GPS 2 (n=47)	*P*-value
Sex, n (%)				0.497
Male	31 (21.5)	78 (54.2)	35 (24.3)	
Female	18 (28.6)	33 (52.4)	12 (19.0)	
Age, n (%)				0.798
<60 years	31 (24.6)	65 (51.6)	30 (23.8)	
≥60 years	18 (22.2)	46 (56.8)	17 (21.0)	
Smoker, n (%)				0.513
No	22 (25.9)	47 (55.3)	16 (18.8)	
Yes	27 (22.1)	64 (52.5)	31 (25.4)	
Pathology, n (%)				0.368
Squamous	11 (17.5%)	40 (63.5%)	12 (19.0%)	
Adenocarcinoma	34 (26.8%)	61 (48.0%)	32 (25.2%)	
Others	4 (23.5%)	10 (58.8%)	3 (17.6%)	
ECOG, n (%)				0.818
0	6 (23.1%)	13 (50.0%)	7 (26.9%)	
1	43 (23.8%)	98 (54.1%)	40 (22.1%)	
Clinical staging, n (%)				0.281
IIIA	5 (20.0)	15 (60.0)	5 (20.0)	
IIIB	17 (35.4)	23 (47.9)	8 (16.7)	
IV	27 (20.1)	73 (54.5)	34 (25.4)	
First-line chemotherapy, n (%)				0.198
G+P	37 (23.1)	88 (55.0)	35 (21.9)	
N+P	2 (14.3)	10 (71.4)	2 (14.3)	
T+P	1 (10.0)	4 (40.0)	5 (50.0)	
MTA+P	9 (39.1)	9 (39.1)	5 (21.7)	
Rescue therapy, n (%)				0.821
Other	22 (26.5%)	42 (50.6%)	19 (22.9%)	
Chemotherapy	22 (22.7%)	52 (53.6%)	23 (23.7%)	
EGFR-TKI	4 (17.4%)	15 (65.2%)	4 (17.4%)	

G, gemcitabine; N, navelbine; T, taxol; MTA, pemetrexed; P, platinum.

interval (95% cCI). A two-tailed *P*-value that was less than 0.05 was considered to be statistically significant.

Results

In total, 207 advanced NSCLC patients who completely met the inclusion criteria were analyzed in this study. Thus, we investigated 144 men and 63 women; the median age of these included subjects was 58 years (range, 35-78 years). As shown in **Table 1**, the clinicopathological characteristics were determined in the GPS subgroup. The three GPS subgroups were similar in terms of age, sex, smoking history, NSCLC pathology, ECOG performance status, clinical staging, first-line chemotherapy regimen, and rescue therapy regimens (all *P*-values > 0.05).

In this study, 134 (64.5%) patients died of NSCLC, and the median OS of advanced NSCLC patients with GPS values of 2, 1, and 0 (**Figure 1**) were 14.3 mo (range, 8.5-20.2 mo), 15.9 mo (13.6-18.2 mo), 19.1 mo (16.6-21.6 mo), respectively. The results of univariate analysis indicated that GPS profile was not significantly associated with OS, even after the patients were treated with platinum-based first-line chemotherapy (both *P*-values >0.05); however, the results of multivariate analysis indicated a totally different situation: compared to patients with GPS of 0, the OS of patients with GPS of 1 was similar (1.59 [0.97, 2.60], P=0.065), while patients with GPS of 2 had a significantly shorter OS (1.75 [1.00, 3.06], P= 0.049; **Table 2**).

Disease progression occurred in 191 (92.3%) patients. The median PFS of advanced NSCLC patients with GPS 2, 1, and 0 (**Figure 2**) were 8.3 mo (6.9-9.7 mo), 8.9 mo (8.0-9.7 mo), 10.5 mo (8.8-12.1 mo), respectively. Univariate and multivariate analyses indicated the following results: compared to patients with GPS 0, patients with GPS 1 had similar PFS (both *P*-values >0.05), while patients with GPS 2 had a significantly shorter PFS (1.73 [1.11, 2.69], P=0.015; 1.71 [1.08, 2.70], P=0.021; **Table 3**).

Discussion

In this experimental study, we used GPS for investigating advanced NSCLC patients. Note that, GPS is a prognostic system that is based

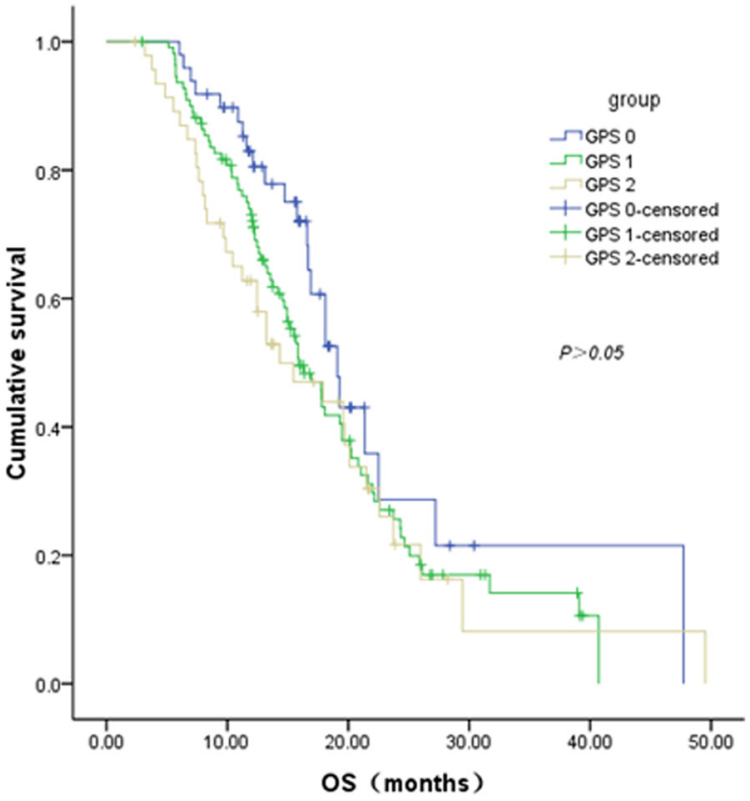

Figure 1. Cumulative OS curves by GPS subgroups.

Table 2. Univariate and multivariate analyses of GPS with OS

	Univariate		Multivariate	
GPS	HR (95% CI)	*P*-value	HR (95% CI)*	*P*-value
0	1.00		1.00	
1	1.45 (0.91-2.31)	0.121	1.59 (0.97-2.60)	0.065
2	1.60 (0.94-2.74)	0.086	1.75 (1.002-3.062)	0.049

*Adjusted by age, sex, smoking status, pathological type, ECOG performance status, clinical stage and first-line chemotherapy regimen.

on systemic inflammatory response and nutritional status; it predicts the survival of patients afflicted with various malignancies [7]. To the best of our knowledge, ours is the first study to report the how GPS was used to predict the survival of advanced NSCLC patients in China considering the effect of target therapy. These patients had received platinum-based first-line chemotherapy. In this study, one of the most important findings was that GPS is an independent prognostic factor that detects poor OS and PFS in these patients. This finding agreed well with the results of previous reports [9, 10, 12, 17].

Scientists have not been able to elucidate the mechanism through which the pathogenetic progression of advanced GPS is associated with poor survival in cancer patients, including those with advanced NSCLC. Host inflammatory response plays a pivotal role in the occurrence and progression of malignant tumors [18-21]. In several previous studies, researchers have proved that an elevated serum CRP is associated with poor prognosis in NSCLC patients [22-25]. A high-level serum CRP is an indicator of a tumor-induced inflammatory response, which may ultimately suppress the antitumor immunity [20, 21]. Moreover, hypoalbuminemia is normally accepted as a good indicator of malnutrition and even cachexia [26-28]. Espinosa *et al.* [29] have reported that serum albumin level is an independent predictor of tumor recurrence in stage I NSCLC patients, who have received radical resection. Jin *et al.* [30] have reported that advanced NSCLC patients with a normal serum albumin level might show a better treatment response to an intensive regimen that primarily consisted of cisplatin. Furthermore, Krzystek-Korpacka *et al.* [31] have reported that in gastrointestinal cancer patients with cachexia as a complication, the GPS level was high. In these patients, there was an elevation in the multiple acute-phase proteins, including interleukins 6 and 8, tumor necrosis factor alpha, vascular epidermal growth factor, and heparin-binding cytokines. These pro-inflammatory cytokines synergistically contributed to metabolic wasting, facilitating disease progression [32, 33].

The use of EGFR TKI, such as gefitinib and erlotinib, has shown to improve the survival of advanced NSCLC patients with specific EGFR mutations [3-5]. In previous reports, one of the major limitations was the fact that although the prognostic role of GPS in advanced NSCLC patients was evaluated, the potential confounding effect of using TKI was not analyzed [8-12].

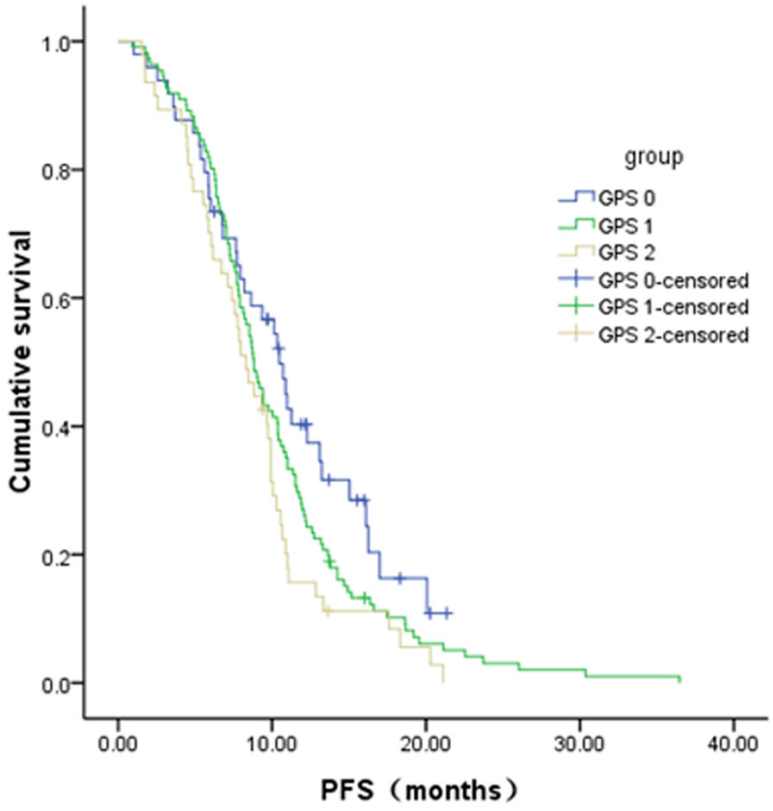

Figure 2. Cumulative PFS curves by GPS subgroups.

Table 3. Univariate and multivariate analyses of GPS with PFS

	Univariate		Multivariate	
GPS	HR (95% CI)	*P-value*	HR (95% CI)*	*P-value*
0	1.00		1.00	
1	1.32 (0.91-1.94)	1.108	1.15 (0.77-1.70)	0.504
2	1.73 (1.11-2.69)	0.015	1.71 (1.08-2.70)	0.021

*Adjusted by age, sex, smoking status, pathological type, ECOG performance status, clinical stage and first-line chemotherapy regimen.

Our results indicate that advanced NSCLC patients with GPS 2, receiving platinum-based first-line chemotherapy, were at a higher risk of disease progression and mortality. Moreover, advanced NSCLC patients with GPS 1 were not as susceptible as those with GPS 0. This finding was independent of age, sex, tumor pathology, clinical staging, chemotherapy regimen, and the use of TKI in rescue therapy. Our study had some limitations. We investigated a small sample of patients, including patients with GPS of 0 and 2. The patients were followed up for a relatively short duration of time. A large-scale study involving long-term follow up is being carried out at our institute in order to further validate the prognostic role of GPS in advanced NSCLC patients, receiving platinum-based first-line chemotherapy as the primary mode of treatment.

Conclusion

In conclusion, GPS is an independent prognostic factor for poor OS and PFS in advanced NSCLC patients of China. In our study, these patients received platinum-based first-line chemotherapy. Patients with GPS 1 had a survival that was similar to those with GPS 0, while patients with GPS 2 were at a higher risk of disease progression and mortality. In advanced NSCLC patients, the underlying inflammatory response was modified. So, we propose that optimum nutrition and balanced diet can improve the chances of survival of these patients.

Disclosure of conflict of interest

None.

Address correspondence to: Wei Li, Cancer Center, First Affiliated Hospital, Jilin University, Changchun 130021, Jilin, China. Tel: +86 431 88782180; Fax: +86 431 88786134; E-mail: 365658791@163.com; Lina Jin, School of Public Health, Jilin University, Changchun 130021, Jilin, China. Tel: 86-431-85645486; Fax: 86-431-85645486; E-mail: jinln@jlu.edu.cn

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