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Evaluation of LIPI and mGPS as prognostic factors in extensive-stage small-cell lung cancer

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Ethics Committee Approval
The study was performed according to the institutional ethical standards (University of Health Sciences, Umraniye Training and Research Hospital, Number: B.10.1.TKH.4.34.H.GP.0.01/367).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: There is an unmet need for effective prognostic models in small cell lung cancer. Lung immune prognostic index (LIPI) and Modified Glasgow Prognostic Score (mGPS) markers are prognostic in various cancers. We aimed to examine LIPI and GPS markers' prognostic effects on overall survival (OS) in extensive-stage small-cell lung cancer (SCLC) patients.

Methods: Patients who were 18 years of age or older, diagnosed with extensive-stage small cell lung carcinoma who received platinum-based chemotherapy as first-line treatment were included in this retrospective observational study. Having concurrent or sequential radiotherapy to the thorax and receiving non-platinum-based chemotherapy as first-line treatment were the criteria for exclusion. We measured their pretreatment LIPI and mGPS markers and performed multivariate Cox regression analyses of progression-free survival (PFS) or OS in extensive stage-SCLC patients.

Results: A total of 129 patients were included in the study. Twenty-eight patients (21.7%) were mGPS 0, 65 patients (50.4%) were mGPS 1, and 36 (27.9%) were mGPS 2. Fourteen percent of the patients were LIPI 0 (n=18), %38 were LIPI 1 (n=49), and %48 were LIPI 2 (n=62). The OS of the mGPS 0, mGPS 1, and mGPS 2 patients were 19.0 months (95% CI, 16.3-21.7), 8.4 months (95% CI, 7.1-9.8), and 6.4 months (95% CI, 3.1-9.6) respectively, and those of LIPI 0, LIPI 1, and LIPI 2 patients were 18.3 months (95% CI, 9.9-26.7), 11.7 months (95% CI, 5.3-18.1), and eight months (95% CI, 6.6-9.5), respectively. In the multivariate analysis, ECOG PS 0-1 and LIPI score 0-1 were associated with better PFS (P=0.035 and P=0.03 respectively) and OS (P=0.003 and P=0.036 respectively).

Conclusions: LIPI score predicted an unfavorable prognosis, whereas mGPS was not associated with survival. It would be better to consider the use of the LIPI score when managing extensive-stage small cell lung cancer.

Keywords: Lung immune index, Small cell, Prognostic factor, Extensive stage, Survival

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Introduction

Small cell lung cancer (SCLC) accounts for approximately 13% -15% of all lung cancers. One-third of the cases are diagnosed with limited disease (LD) and two-thirds, with extensive disease (ED) [1, 2]. Small cell lung cancer is a very chemosensitive tumor, however, the median overall survival (OS) of ED-SCLC is around 10 months. Although extended survival is attempted with various chemotherapeutic agents, the advantage remains limited [3,4]. Studies found that patients' performance status (PS), age, smoking status, and disease stage are prognostic factors [5, 6]. Inflammation and immunity play an essential role in tumor formation, progression, invasion, metastasis, and response to treatment [7]. The survival effect of systemic inflammatory response has rarely been studied in these patients [8].

Lung immune prognostic index (LIPI) is a marker that combines the derived neutrophil-lymphocyte (dNLR) ratio and serum lactate dehydrogenase (LDH) level. Recent studies reported it as a prognostic factor, especially in patients with non-small lung cancer. LIPI was categorized into 3 groups in the studies: Group 0 (favorable) indicates a dNLR of <3 and a normal LDH, group 1 (intermediate) indicates a dNLR of <3 but high LDH and group 2 (poor) indicates a dNLR >3 and a high LDH level [9].

Serum albumin and C-reactive protein (CRP) are routinely examined during SCLC diagnosis. Modified Glasgow Prognostic Score (mGPS) includes the serum albumin and CRP values. Sonehara et al. [10] reported that mGPS had a prognostic effect on SCLC patients' overall survival.

mGPS was categorized into 3 groups, as follows: mGPS group 0: Patients with normal albumin levels (>3.5 g/dl) and CRP (<1.0 mg/dl), mGPS group 1: Patients with normal albumin levels (>3.5 g/dl) and an elevated CRP (>1.0 mg/dl) or a normal CRP (<1.0 mg/dl) with low albumin levels (<3.5 g/dl), and mGPS group 2: Patients with low albumin levels (<3.5 g/dl) and a high CRP (> 1.0 mg/dl).

Our study aimed to examine the prognostic effect of LIPI and GPS markers on overall survival.

Materials and methods

The Ethics Committee approved the study protocol at the University of Health Sciences, Ümraniye Education and Research Hospital, (Date: 22.11.2020, Number: B.10.1.TKH.4.34.H.GP.0.01/367). Eligible patients were aged 18 years of age or older, histopathologically diagnosed with extensive-stage small-cell lung carcinoma, received platinum-based chemotherapy as first-line treatment, and had adequate liver and kidney function. Exclusion criteria were having concurrent or sequential radiotherapy to the thorax and receiving non- platinum-based first-line treatment.

Between 2012 and 2020, a total of 129 patients were recruited from four different institutions.

The baseline characteristics of the patients, namely, age, gender, smoking, performance scores (PS) according to Eastern Cooperative Oncology Group (ECOG), were evaluated. The laboratory values obtained one week before the treatment were as follows: A complete blood count, serum albumin, serum lactate dehydrogenase, serum C-reactive protein, serum creatinine, serum aspartate aminotransferase, and alanine aminotransferase. LIPI and mGPS groups were categorized as previously described. The radiological response to chemotherapy was evaluated according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). Objective response rate (ORR), complete response (CR) + partial response (PR) (ORR: CR + PR) and disease control rate (DCR), ORR + stable disease (SD) (DCR: CR + PR + SD) were calculated. Progression-free survival (PFS) was considered as the time from the date of first chemotherapy initiation to the date of progressive disease documented or death, and overall survival (OS), as the time from the start of the first chemotherapy to death or last follow-up date. OS and PFS were compared between both the LIPI and mGPS groups.

Statistical analysis

The PFS and OS analyses of all SCLC patients were evaluated with the Kaplan-Meier method. Significance tests for PFS and OS were compared using the log-rank test. Univariate and multivariate analyses were performed using the Cox proportional hazard model to determine the independent prognostic factors. The last follow-up date in the present study was 30 September 2020, and a *P*-value of <0.05 indicated statistical significance. Statistical analysis was performed using IBM SPSS Statistics, version 26.

Results

mGPS

A total of 129 patients were included in the study. Twenty-eight patients (21.7%) were mGPS 0, 65 patients (50.4%) were mGPS 1, and 36 (27.9%) were mGPS 2. There were 108 (83.7%) males. One hundred and twenty-six patients (97.7%) smoked. Among mGPS 0 patients, 19 (67.9%) were ECOG PS 0, 8 (28.5%) were ECOG PS 1 and 1 (3.6%) was ECOG PS 2. Among mGPS 1 patients, 15 (23.1%) were ECOG PS 0, 24 (36.9%) were ECOG PS 1, 24 (36.9%) were ECOG PS 2, and 2 (3.1%) were ECOG PS 3. Among mGPS 2 patients, 6 (16.7%) were ECOG PS 0, 9 (25%) were ECOG PS 1, 20 (55.5%) were ECOG PS 2, and 1 (2.8%) was ECOG PS 3 (Table 1).

Table 1: Demographics, and clinical characteristics of mGPS

Characteristic	All patients, n (%)	mGPS		
		0	1	2
Patients	129	28 (21.7)	65 (50.4)	36 (27.9)
Age, years, median (range)	62 (42-82)	61 (42-77)	64 (43-79)	63 (42-82)
Gender				
Male	108 (83.7)	22 (78.6)	59 (90.8)	27 (75)
Female	21 (16.3)	6 (21.4)	6 (9.2)	9 (25)
ECOG PS				
0	40 (31)	19 (67.9)	15 (23.1)	6 (16.7)
1	41 (31.8)	18 (28.5)	24 (36.9)	9 (25)
2	45 (34.9)	1 (3.6)	24 (36.9)	20 (55.5)
3	3 (2.3)	0	2 (3.1)	1 (2.8)
Smoking history				
Current+former	126 (97.7)	28 (100)	62 (95.4)	36 (100)
Never	3 (2.3)	0	3 (4.6)	0
Metastasis				
Brain	18 (14)	4 (14.3)	10 (15.4)	4 (11.1)
Bone	37 (28.7)	14 (50)	14 (21.5)	9 (25)
Liver	42 (32.6)	6 (21.4)	20 (30.8)	16 (44.4)
Pleural	9 (7)	1 (3.6)	2 (3.1)	6 (16.7)
Lymph nodes	24 (18.6)	4 (14.3)	10 (15.4)	10 (27.8)
Adrenal gland	25 (19.4)	3 (10.7)	17 (26.2)	5 (13.9)

While all patients received first-line chemotherapy, second-line chemotherapeutics were administered to 60.7% of the patients in mGPS 0, 30.8% in mGPS 1, and 22.2% in mGPS

2. Third-line chemotherapeutics were administered to 21.4% of patients in mGPS 0, 3.1% in mGPS 1, and 5.6% in mGPS 2 (Table 2). In the first-line chemotherapy response evaluation, ORR was 92.9% in mGPS 0, 52.4% in mGPS 1 and 44.5% in mGPS 2, while DCR was 92.9% in mGPS 0, 55.5% in mGPS 1 and 52.8% in mGPS 2 (Table 3).

Table 2: Treatment content according to mGPS and LIPI

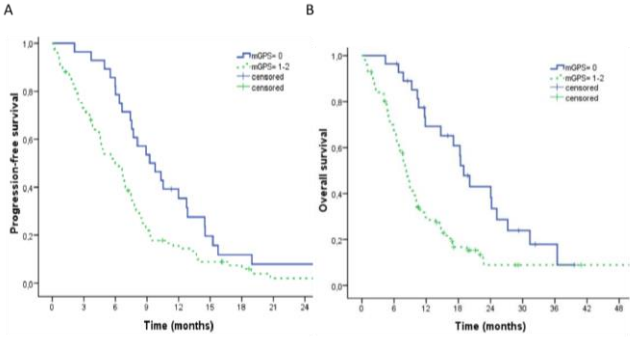
Treatment	All patients	mGPS 0	mGPS 1	mGPS 2	LIPI 0	LIPI 1	LIPI 2
n	129	28	65	36	18	49	62
First-line treatment, n	129	28	65	36	18	49	62
Treatment administration, %	100	100	100	100	100	100	100
Second-line treatment, n	45	17	20	8	10	14	21
Treatment administration, %	34.9	60.7	30.8	22.2	55.6	28.6	33.9
Third-line treatment, n	10	6	2	2	3	3	4
Treatment administration, %	7.8	21.4	3.1	5.6	16.7	6.1	6.5

Table 3: The efficacy of first-line chemotherapy according to mGPS and LIPI

Category	All patients (n=129)	mGPS 0 (n=28)	mGPS 1 (n=65)	mGPS 2 (n=36)	LIPI 0 (n=18)	LIPI 1 (n=49)	LIPI 2 (n=62)
Best overall response, n (%)							
CR	14 (10.9)	8 (28.6)	4 (6.2)	2 (5.6)	1 (5.6)	9 (18.4)	4 (6.5)
PR	62 (48.1)	18 (64.3)	30 (46.2)	14 (38.9)	11 (66.1)	25 (51)	26 (41.9)
SD	5 (3.8)	0	2 (3.1)	3 (8.3)	1 (5.6)	1 (2)	3 (4.8)
PD	48 (37.2)	2 (7.1)	29 (44.5)	17 (47.2)	5 (27.7)	14 (28.6)	29 (46.8)
ORR, %	59	92.9	52.4	44.5	66.7	69.4	48.4
DCR, %	62.8	92.9	55.5	52.8	72.3	71.4	53.2
PFS,months	6.8	9.2	6.3	4.4	7.5	7.5	4.9
(95% CI)	(5.9-7.7)	(6.4-12.1)	(4.9-7.8)	(2.1-6.8)	(5.4-9.6)	(6.1-8.9)	(2.6-7.2)

The PFS of the mGPS 0, mGPS 1, and mGPS 2 patients were 9.2 months (95% CI 6.4-12.1 months), 6.3 months (95% CI 4.9-7.8 months), and 4.4 months (95% CI 2.1-6.8 months), respectively. The median PFS of mGPS 2 patients was not significantly different from those of the mGPS 0 and mGPS 1 patients (4.4 months vs. 9.2 months, P=0.024 and 4.4 months vs. 6.3 months, P=0.967, respectively), but that of the mGPS 0 patients significantly differed from that of the mGPS 1 patients (9.2 months vs. 6.3 months, P=0.006) (Figure 1).

Figure 1: Kaplan-Meier curves according to the modified Glasgow prognostic score (mGPS) in small cell lung cancer (SCLC) patients. (A) The median progression-free survival (PFS) of the mGPS 0 group was significantly longer than those of the mGPS 1 and mGPS 2 groups (9.2 months vs. 6.0 months, respectively, P=0.006). (B) The median overall survival (OS) of the mGPS 0 group was significantly longer than those of the mGPS 1 and mGPS 2 groups (19.0 months vs. 8.3 months, respectively, P<0.001).



The overall OS was 9.6 months (95% CI, 8.3-10.8). The OS of the mGPS 0, mGPS 1, and mGPS 2 patients were 19.0 months (95% CI, 16.3-21.7), 8.4 months (95% CI, 7.1-9.8), and 6.4 months (95% CI, 3.1-9.6) respectively. The median OS of the mGPS 0 patients was significantly different from those of the mGPS 1 and mGPS 2 patients (19.0 months vs. 8.4 months, P<0.001 and 19.0 months vs. 6.4 months, P=0.001, respectively), while that of the mGPS 1 patients was comparable to that of the mGPS 2 patients (8.4 months vs. 6.4 months, P=0.526) (Figure 1).

In the multivariate analyses, the PFS of mGPS 0 patients did not significantly differ from those of mGPS 1 and mGPS2 patients (HR 1.42, 95% CI 0.87-2.31, P= 0.161). mGPS was not an independent prognostic factor for OS (Tables 4, 5).

Table 4: Univariate and multivariate Cox hazard analysis of potential factors associated with PFS

Category		Univariate			Multivariate		
	PFS (months)	HR	95% CI	*P*-value	HR	95% CI	*P*-value
ECOG PS							
0-1/2-3	7.5 vs. 4.4	1.71	1.17-2.49	0.005	1.54	1.03-2.30	0.035
LIPI							
0-1/2	7.5 vs. 4.9	1.64	1.13-2.37	0.008	1.53	1.04-2.24	0.030
mGPS							
0/1-2	9.2 vs. 6.0	1.85	1.18-2.89	0.006	1.42	0.87-2.31	0.161

Table 5: Univariate and multivariate Cox hazard analysis of potential factors associated with OS

Category		Univariate			Multivariate		
	OS (months)	HR	95% CI	*P*-value	HR	95% CI	*P*-value
ECOG PS							
0-1/2-3	11.8 vs. 6.4	2.40	1.61-3.59	< 0.001	1.92	1.25-2.93	0.003
LIPI							
0-1/2	14.5 vs. 8.0	1.54	1.16-2.05	0.002	1.54	1.03-2.31	0.036
mGPS							
0/1-2	19.0 vs. 8.3	1.55	1.20-2.01	< 0.001	1.71	0.99-2.95	0.053

LIPI

Fourteen percent of patients were LIPI 0 (n=18), 38% were LIPI 1 (n=49), and 48% were LIPI 2 (n=62). Among LIPI 0 patients, 11 (61.1%) were ECOG PS 0, 5 (27.8%) were ECOG PS 1, 1 (5.6%) was ECOG PS 2, and 1 (5.6%) was ECOG PS 3. Among LIPI 1 patients, 14 (28.6%) were ECOG PS 0, 18 (36.7%) were ECOG PS 1, and 17 (34.7%) were ECOG PS 2. Of the LIPI 2 patients, 15 (24.2%) were ECOG PS 0, 18 (29%) were ECOG PS 1, 27 (43.5%) were ECOG PS 2, and 2 (3.2%) were ECOG PS 3 (Table 6).

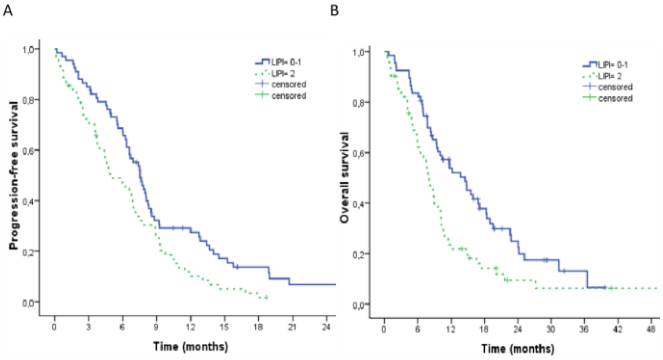
Table 6: Demographics, and clinical characteristics of patients in LIPI groups

Characteristic	LIPI, n (%)		
	0	1	2
Patients	18 (14.0)	49 (38.0)	62 (48.0)
Age, years, median (range)	62 (42-77)	62 (43-79)	63 (42-82)
Gender			
Male	15 (83.3)	40 (81.6)	53 (85.5)
Female	3 (16.7)	9 (18.4)	9 (14.5)
ECOG PS			
0	11 (61.1)	14 (28.6)	15 (24.2)
1	5 (27.8)	18 (36.7)	18 (29.0)
2	1 (5.6)	17 (34.7)	27 (43.5)
3	1 (5.6)	0	2 (3.2)
Smoking history			
Current + former	17 (94.4)	48 (98.0)	61 (98.4)
Never	1 (5.6)	1 (2.0)	1 (1.6)
Metastasis			
Brain	0	7 (14.3)	11 (17.7)
Bone	8 (44.4)	10 (20.4)	19 (30.6)
Liver	5 (27.8)	16 (32.7)	21 (33.9)
Pleural	1 (5.6)	4 (8.2)	4 (6.5)
Lymph nodes	2 (11.1)	8 (16.3)	14 (22.6)
Adrenal gland	3 (16.7)	8 (16.3)	14 (22.6)

While all patients received first-line chemotherapy, second-line chemotherapeutics were administered to 55.6% of the patients in LIPI 0, 28.6% in LIPI 1, and 33.9% in LIPI 2. Third-line chemotherapeutics were given to 16.7% of patients in LIPI 0, 6.1% in LIPI 1, and 6.5% in LIPI 2 (Table 2). In first-line treatment response assessment, the ORR was 66.7% in LIPI 0, 69.4% in LIPI 1, and 48.4% in LIPI 2, while the DCR was 72.3% in LIPI 0, 71.4% in LIPI 1, and 53.2% in LIPI 2 (Table 3).

The PFS of LIPI 0, LIPI 1, and LIPI 2 patients were 7.5 months (95% CI 5.4-9.6 months), 7.5 months (95% CI 6.1-8.9 months), and 4.9 months (95% CI 2.6-7.2 months), respectively. The LIPI 0 group's median PFS was not significantly different from those of the LIPI 1 and LIPI 2 groups (7.5 months vs. 7.5 months, P=0.575 and 7.5 months vs. 4.9 months, P=0.078, respectively). The LIPI 2 group's median PFS significantly differed from that of the LIPI 1 group (4.9 months vs. 7.5 months, P=0.015) (Figure 2).

Figure 2: Kaplan-Meier curves according to the lung immune prognostic index (LIPI) in small cell lung cancer (SCLC) patients. (A) The median progression-free survival (PFS) of the LIPI 0 and LIPI 1 groups were significantly longer than that of the LIPI 2 group (7.5 months vs. 4.9 months, respectively, *P*=0.008). (B) The median overall survival (OS) of the LIPI 0 and LIPI 1 group was significantly longer than that of the LIPI 2 group (14.5 months vs. 8.0 months, respectively, *P*=0.002).



The OS of LIPI 0, LIPI 1, and LIPI 2 patients were 18.3 months (95% CI, 9.9-26.7), 11.7 months (95% CI, 5.3-18.1), and 8 months (95% CI, 6.6-9.5) respectively. The LIPI 2 group's median OS was significantly different from those of the LIPI 0 and LIPI 1 groups (8.0 months vs. 18.3 months, *P*=0.011 and 8.0 months vs. 11.7 months, *P*=0.015, respectively), while that of the LIPI 0 group was comparable to that of the LIPI 1 group (18.3 months vs. 11.7 months, *P*=0.441) (Figure 2).

In the multivariate analysis, ECOG PS 0-1 and LIPI score 0-1 were correlated with better PFS (*P*=0.035 and *P*=0.03 respectively) and OS (*P*=0.003, and *P*=0.036 respectively) (Tables 4, 5).

Discussion

In our study, while the LIPI score was an independent prognostic factor in both PFS and OS in extensive-stage small cell lung cancer, mGPS was not a significant independent prognostic factor of survival.

In their study, Sonehara et al. [10] evaluated whether high mGPS predicts poor survival and reported that mGPS was not prognostic in limited-stage small-cell lung cancer. Similarly, in the research conducted by Fan et al. [11] on operable and inoperable NSCLC patients, although mGPS was significant in the univariate analysis, it proved otherwise in the multivariate analysis.

Zhou et al. [12] investigated the effect of systemic inflammation markers (such as mGPS, CRP/albumin, albumin/globulin, and prognostic nutritional index) on small cell lung cancer prognosis. They stated that all markers were independent risk factors in patients with extensive-stage disease, but this effect was not observed in limited-stage disease. Similarly, mGPS was prognostic in the study performed by Zhou et al. [8]. Minami et al. [13] examined the prognostic effect of pretreatment GPS and the prognostic nutritional index (PNI) markers on OS and PFS in small cell lung cancer patients. GPS and PNI markers were not significant in terms of PFS in the multivariate analysis. To the best of our knowledge, the mGPS has not been investigated in terms of chemotherapy effect (PFS) in small cell lung cancer, except for Minami et al.'s study.

In our study, although mGPS significantly affected both PFS and OS in univariate analysis, multivariate analysis did not yield significant results in terms of OS. However, the p score was remarkably close to significance**.** The lack of homogeneity due to the small number of patients in the groups may be responsible for this finding. Similar to the literature, ECOG PS was a poor prognostic factor in our multivariate analysis.

Studies evaluating the LIPI were generally conducted on non-small cell lung cancer. In these studies, the LIPI score was a significant prognostic factor in terms of OS [9, 14]. In the study conducted by Minami et al. [14], LIPI was assessed in patients with metastatic lung adenocarcinoma. It was an independent prognostic factor in patients who received tyrosine kinase therapy and systemic chemotherapy. In this study, LIPI was of no significance in the group with squamous histology.

There is no sufficient data on the LIPI marker in extensive-stage small-cell lung cancer in the literature. In the first study conducted by Sonehara et al. [10], in which the LIPI score was evaluated, LIPI was an independent risk factor for both PFS and OS in extensive-stage disease. The second study, conducted by Galvano et al. [15], evaluated LIPI and other immune markers in patients with extensive-stage lung neuroendocrine carcinoma. Although the LIPI was numerically different between the groups in terms of its effect on OS, the prognostic effect was not significant.

Similar to the literature, LIPI was a prognostic factor for both OS and PFS in our study.

Inflammation and immunity play an essential role in tumor formation, progression, spread, metastasis, and response to systemic treatment [7]. In recent years, especially in lung cancer, immune checkpoint inhibitors gained an essential role in treatment.

In the IMpower-133 study, both PFS and OS were lengthened with the addition of atezolumab to systemic chemotherapy (carboplatin + etoposide) in the first series in extensive-stage small cell lung cancer [16].

It can be predicted that markers such as LIPI may help predict response to treatment with immune checkpoint inhibitors, where immune markers are essential.

Limitations

Selection bias was inevitable given the retrospective nature of the work. Additionally, the size of the patient population was relatively small.

Conclusion

In our study involving extensive-stage small cell lung cancer patients, LIPI and mGPS were both assessed for their prognostic effects. LIPI score predicted an unfavorable prognosis. It would be better to consider using the LIPI score in managing extensive-stage small cell lung cancer.

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