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Research article

Prognostic scores in pulmonary large cell neuroendocrine carcinoma: A retrospective cohort study

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ABSTRACT

Introduction: Pulmonary large cell neuroendocrine carcinoma (PLCNEC) is a rare but aggressive subtype of lung cancer with an incidence of approximately 3 %. Identifying effective prognostic indicators is crucial for guiding treatments. This study examined the relationship between inflammatory markers and PLCNEC patient overall survival (OS) and sought to determine their prognostic significance in PLCNEC.

Methods: Patients diagnosed with PLCNEC between 2007 and 2022 at the oncology center, were retrospectively included. Patients who underwent surgery were pathologically re-staged post-surgery. Potential prognostic parameters (neutrophil/lymphocyte ratio, platelet/lymphocyte ratio [PLR], panimmune inflammatory value, prognostic nutritional index and modified Glasgow prognostic score [mGPS]) were calculated at that time of diagnosis.

Results: Sixty patients were included. The median follow-up was 23 months. Thirty-eight patients initially diagnosed with early or locally advanced. The mGPS was identified as a poor prognostic factor that influenced disease free survival (DFS) fourfold ($p = 0.03$). All patients' median OS was 45 months. Evaluating factors affecting OS in all patients, statistically significant relationships were observed between OS and the prognostic nutritional index ($p = 0.001$), neutrophil/lymphocyte ratio ($p = 0.03$), platelet/lymphocyte ratio ($p = 0.002$), and pan-immunoinflammatory value ($p = 0.005$). Upon multivariate analysis, the platelet/lymphocyte ratio was identified as an independent poor prognostic factor for OS, increasing the mortality risk by 5.4 times ($p = 0.002$).

Conclusion: mGPS was significantly linked with prognosis in non-metastatic PLCNEC, with patients with higher mGPS exhibiting poorer long-term DFS. This finding contributes to the evolving understanding of PLCNEC. The multivariable predictive model we employed suggests that PLR is

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an independent predictor of OS at all stages. A lower PLR was correlated with worse overall survival. Thus, PLR can be a readily accessible and cost-effective prognostic factor in PLCNEC patients.

1. Introduction

Pulmonary large cell neuroendocrine carcinoma (PLCNEC) is a rare but aggressive subtype of lung cancer with an incidence of approximately 3 % [1]. Following the 2015 revision by the World Health Organization (WHO), PLCNEC was reclassified as a lung neuroendocrine tumor, distinguished from small cell lung cancer (SCLC) [2]. According to analysis of the Surveillance, Epidemiology, and End Results (SEER) database, the 3-year overall survival (OS) and 5-year OS rates for PLCNEC are 22.8 % and 16.8 %, respectively [3]. Survival rate in operated patients remains low; reported 5-year OS is between 10 % and 30 % [4–6].

Due to its rarity, a standard treatment for PLCNEC has yet to be established [7]. American Society of Clinical Oncology guidelines recommend the platinum-etoposide chemotherapy regimen as the most appropriate treatment [8] administered post-diagnosis. However, the effectiveness of this regimen is also suboptimal [9].

Many studies have shown that systemic inflammation and nutritional status are significantly associated with cancer incidence, disease progression, treatment and prognosis [10,11]. Over the last decade, ratios such as C-reactive protein/albumin ratio and albumin/globulin ratio have been shown to be associated with the prognosis of non-small cell lung cancer (NSCLC) patients [12,13]. Elevated pre-treatment neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and decreased lymphocyte/monocyte ratio (LMR) are closely associated with a poor prognosis of NSCLC [14].

Another index, the modified Glasgow prognostic score (mGPS), is calculated based on C-reactive protein and albumin and classified as 0, 1, or 2 [15]. Patients with high C-reactive protein levels (>0.5 mg/dl) and hypoalbuminemia (<3.5 g/dl) are classified as mGPS 2, those with only high C-reactive protein levels are categorized as mGPS 1, those with normal C-reactive levels are categorized as mGPS 0 [16]. The prognostic value of mGPS has been extensively validated in various cancers, including pancreatic, esophageal, gynecologic cancers and renal cell carcinoma [17–20]. To date, the prognostic role of mGPS in PLCNEC patients is uncertain.

The role of inflammatory markers in PLCNEC and neuroendocrine tumors in general has rarely been investigated. Identifying effective prognostic indicators is crucial for guiding treatments. This study examined the relationship between survival and inflammatory markers in patients with PLNEC and tried to determine their prognostic significance in PLNEC.

2. Materials and methods

2.1. Patients characteristics

Patients diagnosed with PLCNEC between 2007 and 2022 at the Kartal Dr. Lütfi Kırdar City Hospital oncology center, were retrospectively included in our study.

Patients who underwent surgery were pathologically re-staged post-surgery according to the TNM staging of the AJCC UICC 8th edition [21]. The metastatic regions of de novo metastatic patients were examined. Data on age, gender, tumor location, tumor stage, diagnostic procedure, surgical procedure, smoking status, laboratory test results at the time of diagnosis, adjuvant treatment status, treatment response, and survival were obtained from patient files.

Potential prognostic parameters were calculated from the blood test results taken at that time of diagnosis. These calculations were: NLR = absolute neutrophil count/total lymphocyte count, PLR = absolute platelet count/absolute lymphocyte count, PNI = serum albumin (g/dL) + (5 x total lymphocyte count), PIV = total neutrophil x platelet x monocyte/lymphocyte count. The mGPS score was calculated using the patients' CRP and albumin values.

2.2. Statistical analysis

Statistical analyses were conducted using "IBM SPSS Statistics for Windows, Version 25.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA)." Descriptive statistics were presented as Mean ± SD, median (IQR) for continuous variables, and n and % for categorical variables. Overall survival (OS) was defined as the time from diagnosis to last contact or death. Disease-free survival (DFS) was defined as the time from PLCNEC operation to the date of last outpatient follow-up or the date of radiological recurrence. Kaplan-Meier analysis was used to compare disease-free survival and overall survival with clinical parameters. The effect of prognostic factors on survival was evaluated using the univariate log-rank test. The hazard ratio (HR) was calculated with a 95 % confidence interval (CI). Multivariate analysis was conducted using the Cox proportional hazards model to assess the effect of prognostic factors on survival. A logistic regression model was employed for multivariate and univariate analysis to evaluate the prognostic factors influencing recurrence. The significance level was accepted as ≤ 0.05.

Ethical approval

Local ethics committee approval was obtained for this study and was conducted in accordance with the Declaration of Helsinki principles. Ethics/Institutional Review Board approval of research—Kartal Dr. Lütfi Kırdar City Hospital, Istanbul, Turkey, Number:

2023/514/244/7, dated February 22, 2023.

3. Results

3.1. Baseline clinical and Demographic findings

A total of 60 patients were enrolled in the study. The clinical features are detailed in Table 1. The median age at presentation was 61, ranging from 41 to 79. Of the participants, 53 (88 %) were male, and 51 (85 %) had a history of smoking. On average, the patients had smoked 45 pack-years. The primary tumor location for 38 patients was in the right lung. At that time of diagnosis, the median SUVmax uptake of the primary lesion on PET/CT was 12, ranging from 5 to 31. As for local treatment, 38 patients underwent primary surgery, while two received cyber radiotherapy.

3.2. Early or locally advanced (stage I-III)

The study included 38 patients who were initially diagnosed with early or locally advanced (Stage I-III) PLCNEC and underwent complete resection. Among these operated patients, 34 underwent lobectomy, 2 underwent pneumonectomy, and 2 underwent bilobectomy. Five of these patients were stage 1 and did not receive adjuvant treatment, and 33 patients received adjuvant chemotherapy. Of the patients receiving adjuvant chemotherapy, 19 received a cisplatin and etoposide regimen, and all regimens were platinum-based. Among the operated patients, 21 (55 %) experienced a recurrence, while the rest remained remission. There was no statistically significant difference in DFS between those who received adjuvant therapy and those who did not. The median time to DFS was 21 months, with 1-year and 3-year DFS rates of 65.0 % and 43.0 %, respectively (Fig. S1).

In the subgroup analysis by stage, median DFS for stage 1 was not reached. Median DFS for stage 2 was 21 months (95 %CI:

Table 1
Baseline clinical features of 60 patients with PLCNEC.

Variables (n=60)	n, (%)
Age (median)	61 (min 41-max 79)
ECOG PS	
0	26 (43)
1–2	34 (57)
Gender	
Female	7 (12)
Male	53 (88)
Smoking status	
Ex-smoker	0 (0.0)
Active smoker	51 (85)
Never	4 (7)
Unknown	5 (8)
Cigarette pack/year (n=51)	45 (min 4-max 90)
Primary localisation	
Right	38 (63)
Left	22 (37)
Diagnostic procedure	
Broncoscopy	7 (12)
Ebus-TBNA	3 (5)
Primary surgery	25 (42)
Trucut FNAB	14 (23)
Other[a]	11 (18)
Primary lesion PET-CT SUV MAX (median)	12 (min 5-max 31)
Local treatment	
Surgery	38 (63)
SBRT	2 (4)
No	20 (33)
TNM stage	
1	11 (18)
2	14 (23)
3	13 (22)
4	22 (37)
Status	
Exitus	27 (45)
Aliver	33 (55)

ECOG: PS, Eastern Corporation Oncology Group Performance Status; EBUS: Endobronchial ultrasonography-guided transbronchial fine-needle aspiration; FNAB: fine needle aspiration biopsy.

[a] Biopsy taken from metastatic tissue; SBRT: stereotactic body radiotherapy; TNM: tumor-node-metastasis staging system.

1.3–40.6), while median DFS for stage 3 was 14 months (95 %CI: 8.3–19.6). The treatment characteristics and outcomes of the non-metastatic group are summarized in Table 2.

When examining the relationship between patients' stages and DFS, it was observed that as the stage increased, the median DFS decreased. However, it was not statistically significant (p = 0.59) (Fig. S2).

In non-metastatic patients, factors affecting DFS were investigated. In the univariable analysis, no association was found between DFS and gender, age, ECOG performance score, SUVmax value of the primary lesion on initial PET-CT, PLR, NLR, PNI, and PIV. The mGPS score was identified as a poor prognostic factor that influenced DFS fourfold, and this relationship was statistically significant (p = 0.03) (Table 3).

In patients with an mGPS of 0, the median DFS was 19 months (95 % CI: 0.00–40.08). For patients with an mGPS of 1, the median DFS was not reached, while for those with an mGPS of 2, the median DFS was eight months (95 % CI: 0.00–48.58) (p = 0.045) (Fig. 1).

3.3. Overall stages

The median follow-up was 23 months, ranging from 1 to 112 months. All patients' median OS was 45 months (95 %CI: 17.5–72.4).

Table 2
Treatment characteristic and outcomes (Non-metastatic group).

	n, (%)
Surgery Type (n=38)	
Lobectomy	34 (90)
Pneumonectomy	2 (5)
Bilobectomy	2 (5)
Pathologic Stage (n=38)	
T1	12 (32)
T2	14 (37)
T3	9 (24)
T4	3 (7)
N0	31 (82)
N1	6 (16)
N2	1 (2)
Pathologic tumor diameter (cm)(median)	3.5 (0.6–12.5)
Pleural invasion (n=33)	
Present	19 (58)
Absent	14 (42)
Vascular invasion	
Present	10 (27)
Absent	28 (73)
Lymphatic invasion	
Present	9 (24)
Absent	29 (76)
Adjuvant treatment	
Yes	33 (87)
No	5 (13)
Adjuvan Cht Regimen	
Cisplatin/Etoposide	19 (58)
Carboplatin/Etoposide	6 (18)
Cisplatin/Navelbine	4 (12)
Carboplatin/Taxane	4 (12)
Recurrence status	
Present	17 (45)
Absent	21 (55)
Stage 1 disease free survival	
Median (Months)	Non reached
12 months rate	70
24 months rate	70
Stage 2 disease free survival	
Median (Months)	21 (95 %CI:1.3–40.6)
12 months rate	60
24 months rate	40
Stage 3 disease free survival	
Median (Months)	14 (95 %CI:8.3–19.6)
12 months rate	66
24 months rate	41
Total disease free survival	
Median (Months)	21 (95 %CI:0–45.3)
12 months rate	65
24 months rate	43

Cht: chemotherapy. Disease-free survival was calculated using Kaplan-Meier analysis.

Table 3
Univariate analysis of patients with nonmetastatic for disease-free survival (DFS) according to clinico-pathological factors.

n=38	Univariate analysis	
	HR (95 %CI)	p
Age	1.9 (0.7–5.2)	0.19
<65		
≥65		
ECOG PS	1.02 (0.3–2.6)	0.96
0		
1–2		
Primary lesion PET-CT SUV MAX	2.6 (0.7–8.8)	0.11
>12		
≤12		
Pathologic T stage	1.0 (0.3–2.6)	0.98
T 1-2		
T 3-4		
Pathologic N stage	1.01 (0.2–3.5)	0.98
N0		
N 1-2		
Pathologic Stage	2.02 (0.5–7.02)	0.26
1		
2–3		
Pathologic T diameter	1.07 (0.3–2.9)	0.88
≥3.5 cm		
<3.5 cm		
Vascular invasion	1.04 (0.3–2.9)	0.93
Present		
Absent		
Lymphatic invasion	2.2 (0.7–6.6)	0.14
Present		
Absent		
Pleural invasion	0.54 (0.1–1.6)	0.54
Present		
Absent		
NLR	1.9 (0.5–5.4)	0.22
<2.4		
≥2.4		
PLR	1.4 (0.5–3.8)	0.39
<127.1		
≥127.1		
PNI	0.4 (0.1–1.5)	0.21
<42.1		
≥42.1		
PIV	0.94 (0.3–2.5)	0.94
<343.9		
≥343.9		
mGPS	4.3 (1.09–17.5)	**0.03**
0–1		
2		

ECOG: PS, Eastern Corporation Oncology Group Performance Status; TNM: tumor-node-metastasis staging system; NLR: total nötrofil-lenfosit ratio; PLR: total platelet-lymphocyte ratio; PNI: prognostic nutritional index; PIV: pan immun inflammatory value; mGPS: modified Glasgow Prognostic Score; HR: hazard ratio; CI: confidence interval. Statistically significant *p* values are written in bold. Analysis was performed using the Cox proportional hazards model to evaluate the effect of prognostic factors on DFS.

There were 27 (46 %) deaths due to disease progression. The median time to OS had 1-year and 3-year OS rates of 74.0 % and 42.0 %, respectively (Table 4).

In a subgroup analysis based on stages, the median OS for stage 1 was 92 months (95 %CI: 46.6–137.3). For stage 2, the median OS was 62 months (95 %CI: not calculated). For stage 3, the median OS was 45 months (95 %CI: 34.4–55.5), and for stage 4, the median OS was 11 months (95 %CI: 6.1–15.8) (Table 4). The 1-year and 3-year survival outcomes based on stages are presented in Table 4. When examining the relationship between stages and OS, a statistically significant finding ($p < 0.001$) was observed, indicating that as the stage advanced, the overall survival decreased (Figs. S3 and S4).

Evaluating factors affecting overall survival in all patients, parameters found significant in univariate analyses were further examined in multivariate analyses. The univariate analysis found no association between overall survival and gender, age, ECOG performance score, SUVmax value of the primary lesion on initial PET-CT, and the mGPS. However, statistically significant relationships were observed between overall survival and the prognostic nutritional index ($p = 0.001$), NLR ($p = 0.03$), PLR ($p = 0.002$), and pan-immunoinflammatory value ($p = 0.005$).

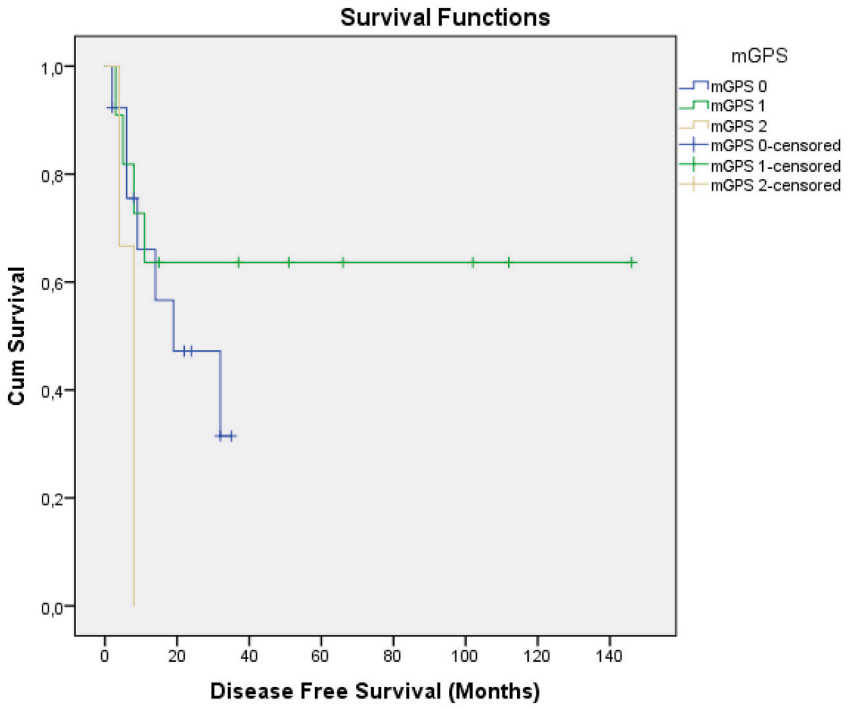

Fig. 1. Disease Free Survival graphic in the nonmetastatic group according to mGPS score.

Table 4
Overall survival of whole group.

Whole group	
Median (Months)	45 (95 %CI:17,5–72,4)
12 months OS (%)	74
60 months OS (%)	42
Stage 1	
Median (Months)	92 (95 %CI:46,6–137,3)
12 months OS (%)	90
60 months OS (%)	50
Stage 2	
Median (Months)	62 (95 %CI: not calculated)
12 months OS (%)	76
36 months OS (%)	49
Stage 3	
Median (Months)	45 (95 %CI:34.4–55.5)
12 months OS (%)	91
60 months OS (%)	38
Stage 4 (de-novo metastasis)	
Median (Months)	11 (95 %CI: 6.1–15.8)
12 months OS (%)	48
60 months OS (%)	16

Overall survival was calculated using Kaplan-Meier analysis. OS: overall survival; HR: hazard ratio; CI: confidence interval.

Upon multivariate analysis, the platelet to lymphocyte ratio was identified as an independent poor prognostic factor for OS, increasing the mortality risk by 5.4 times (HR: 5.4 (95 %CI: 1.8–16.1), $p = 0.002$) (Table 5).

In the ROC analysis performed to determine the optimal cut-off point of PLR, the median PLR was calculated as 142.05 as there was no cut-off point. While median OS could not be reached in patients with PLR< 142.05, median OS was 28 months (95 % CI 14.3–41.7) in patients with PLR ≥142.05 ($p < 0.001$) (Fig. 2).

4. Discussion

PLCNEC, even when resected at an early stage, has a poor prognosis, and it continues to be debated whether this tumor should be

Table 5
Cox regression analysis – Overall Survival.

	Univariate analysis		Multivariate analysis	
	HR (95 %CI)	p	HR (95 %CI)	p
Gender				
Female	2.7 (0.3–20.5)	0.32		
Male				
Age				
≤65	0.79 (0.3–1.7)	0.79		
>65				
ECOG PS				
0	1.8 (0.8–4.08)	0.15		
1–2				
Primary lesion PET-CT SUV MAX				
≥12	1.9 (0.7–4.8)	0.15		
<12				
Stage at diagnosis				
Stage 1–3	5.4 (2.2–12.8)	<0.001		
Stage 4				
NLR				
<2.63	2.5 (1.04–6.1)	0.03		
≥2.63				
PLR				
<142.05	4.7 (1.7–12.4)	0.002	5.4 (1.8–16.1)	**0.002**
≥142.05				
PNI				
<42.01	0.2 (0.1–0.7)	0.001		
≥42.01				
PIV				
<505.7	3.8 (1.4–9.8)	0.005		
≥505.7				
mGPS				
0–1	1.9 (0.7–5.04)	0.18		
2				

ECOG: PS, Eastern Corporation Oncology Group Performance Status; NLR: total neutrophil-lymphocyte ratio; PLR: total platelet-lymphocyte ratio; PNI: prognostic nutritional index; PIV: pan immun inflammatory value; mGPS: modified Glasgow prognostic score; HR: hazard ratio, CI: confidence interval. Statistically significant *p* values are written in bold. Analysis was performed using the Cox proportional hazards model to evaluate the effect of prognostic factors on survival.

treated in the same way as NSCLC or SCLC. For early-stage PLCNEC patients, surgical intervention is predominantly employed, and chemotherapy with platinum and etoposide can reduce the likelihood of recurrence [22]. Given the generally unfavorable prognosis, adjuvant chemotherapy might present the best opportunity to enhance survival irrespective of the stage [23]. The study, which included 221 patients with completely resected stage I to IIIA high-grade lung neuroendocrine carcinoma in Japan, found comparable three-year progression-free survival (PFS) rates between etoposide versus cisplatin and irinotecan and cisplatin in the subgroup of 104 patients with LCNEC [24]. In our study, among the 38 operated patients, those who received adjuvant treatment had a noticeably longer DFS numerically compared to those who did not, but this difference was not statistically significant. The rarity of this subtype might have rendered our sample size insufficient to demonstrate this difference. No differences were observed between chemotherapy regimens, subgroup stage analyses, and the relationship between pathological tumor size and DFS.

Veronesi et al. examined 144 LCNEC patients in a multicenter study. All of these patients, whose average age was 63 and were mostly men, underwent surgery. Consistent with literature reports, all were smokers, 93 % of whom were men [23]. Most were diagnosed with early-stage disease (50 % stage I, 20 % stage II) and the 5-year survival rate was 42.5 %. Veronesi et al. observed that OS rates for all stages of patients ranged from 0 % to 57 % at five years in 12 different studies. In their study, multivariate analysis revealed that stage III disease, age, and type of surgery were independent prognostic factors for OS. Contrary to literature findings, in our study, only 38 patients underwent surgery, with the remaining 22 diagnosed at the metastatic stage via biopsy. When examining the relationship between stages and DFS among operated patients, although the median DFS decreased as the stage advanced, no statistically significant difference was founded ($p = 0.59$).

The prognostic value of mGPS is well-defined across various cancer types. In 25 studies of 4629 patients, Wu et al. found a significant association between high mGPS and poor OS in pancreatic cancer patients (HR = 1.92, 95 % CI: 1.60–2.30, $P < 0.002$) [20]. Wang et al. an analysis of 3415 cases across ten studies also revealed a significant association between high mGPS and poor OS (HR = 1.66, 95 % CI: 1.14–2.41, $P = 0.008$) in esophageal cancer patients [15]. In another meta-analysis by Chen et al. examining 2047 patients from seven relevant studies, mGPS was shown to be an independent risk indicator for poor prognosis in hepatocellular carcinoma patients (HR = 2.21, 95 % CI: 1.73–2.82) [25].

In lung cancer, the predictive role of mGPS on patient prognosis was investigated in two meta-analyses. Zhang et al. studied 1164 patients with advanced lung cancer receiving immune checkpoint inhibitors; higher mGPS was associated with worse OS (HR = 4.61, 95 % CI: 1.25–16.99, $P = 0.022$) and PFS (HR = 2.61, 95 % CI: 1.28–5.34, $P = 0.008$) [26]. Another meta-analysis by Jin et al. found

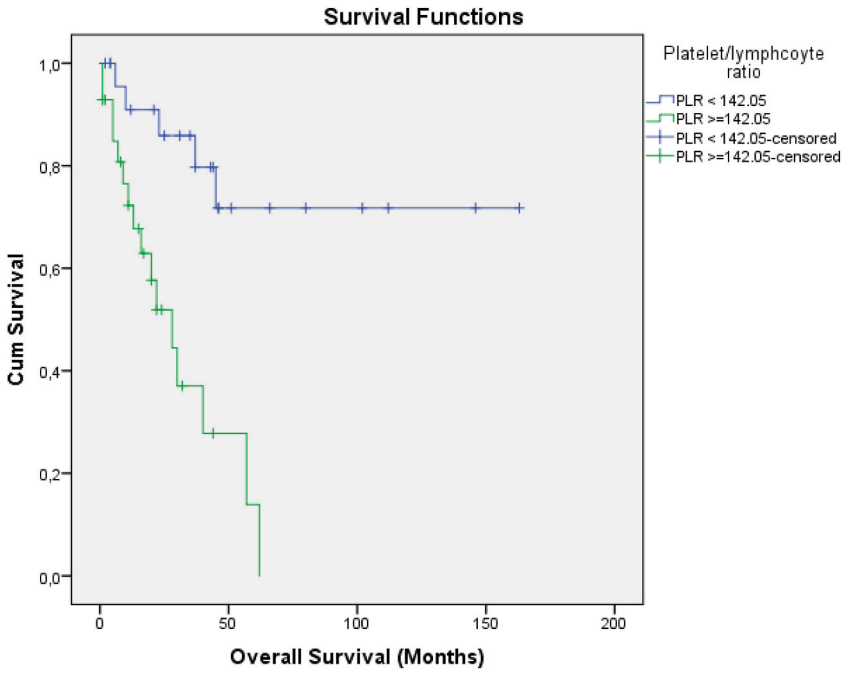

Fig. 2. Relationship between PLR and overall survival in the whole group
PLR: total platelet-lymphocyte ratio. Overall survival was calculated using Kaplan-Meier analysis.

that high mGPS predicted OS in all lung cancer patients (HR = 1.77, 95 % CI: 1.35–2.31, P < 0.05), however a non-significant correlation between mGPS and OS was observed in operated patients (HR = 2.48, 95 % CI: 0.90–6.85, P = 0.079) [27]. In our study, patients with mGPS scores of 0 and 1 experienced delayed recurrence, while those with a score of 2 had a shorter median DFS. In operated patients, the mGPS was determined to be a poor prognostic factor that affected DFS fourfold, and this relationship was statistically significant (p = 0.03). To our knowledge, this is the first study examining the relationship between mGPS and PLCNEC prognosis.

In Okui M. et al.'s study, only NLR at diagnosis showed significant differences between subgroups of PNETs, but PLR and LMR showed significant prognostic value for PNETs. The ROC analysis determined the optimal cut-off points for PLR, NLR and LMR as 152.5, 2.5 and 2.9, respectively. Low pre-treatment LMR, high pre-treatment PLR, and NLR were associated with worse PFS and OS [28]. In a study examining 106 PLCNEC patients, patients with high PLR or NLR had a lower survival than those with low PLR (HR = 2.086, 95 % CI: 1.279–3.402, p = 0.003) or NLR (HR = 2.46, 95 % CI: 1.508–4.011, P < 0.001). In multivariate survival analysis, T stage and NLR (P < 0.001) were important for the prognosis of LCNEC patients [29]. NLR is not significantly associated with the outcome of metastatic LCNEC under chemotherapy [30], therefore systemic inflammation appears to have a stronger prognostic effect in case of early compared to advanced disease. In our study, for overall stages, a statistically significant relationship was found between NLR (p = 0.03), PNI (p = 0.001), PIV (p = 0.005), PLR (p = 0.002), and overall survival. As a result of multivariate analysis, low PLR was determined to be an independent poor prognostic factor for overall survival, increasing the risk of mortality by 5.4 times (HR: 5.4 (1.8–16.1), p = 0.002).

The precise mechanism of tumor prognosis influenced by easily obtainable, inexpensive tests like hemogram and albumin, such as PLR, NLR, and PIV, remains unclear. Further studies are needed to understand the molecular basis of these results. Inflammation in the tumor microenvironment can influence tumor development, progression, and treatment response in various ways [31]. In future studies, inflammatory cells may be combined to direct the efficacy of chemotherapy or immunotherapy.

There are limitations in our study. First, all included studies were retrospective. The sample size was small, which might introduce bias.

5. Conclusion

PLCNECs are an exceptionally heterogeneous and rare group of tumors characterized by distinct clinical presentations, pathological features, and prognoses. Due to the infrequency of PLCNEC, it is difficult to conduct studies with a large cohort. In our study, we gathered data from 60 PLCNEC patients spanning fifteen years and unveiled that pre-treatment PLR and mGPS could be predictive factors for disease-free survival and overall survival in PLCNEC. Notably, mGPS was significantly linked with prognosis in non-metastatic LCNEC, with patients with higher mGPS exhibiting poorer long-term DFS. This finding contributes to the evolving understanding of PLCNEC. The multivariable predictive model we employed suggests that PLR is an independent predictor of OS at all stages. A lower PLR was correlated with worse overall survival. Thus, PLR can be a readily accessible and cost-effective prognostic

factor in PLCNEC patients. To validate the prognostic significance of PLR, future studies, ideally prospective and with larger sample sizes, are imperative.

Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Goncagul Akdag: Writing – review & editing, Writing – original draft, Supervision, Project administration, Conceptualization. **Özkan Alan:** Project administration. **Akif Dogan:** Data curation. **Sedat Yildirim:** Resources, Data curation. **Oguzcan Kinikoglu:** Writing – review & editing. **Aziz Batu:** Data curation. **Emre Kudu:** Methodology. **Gonca Gül Geçmen:** Data curation. **Deniz Isik:** Writing – review & editing. **Ozlem Nuray Sever:** Writing – review & editing. **Hatice Odabas:** Supervision. **Mahmut Emre Yildirim:** Supervision. **Nedim Turan:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

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References

[1] M. Fasano, et al., Pulmonary large-cell neuroendocrine carcinoma: from Epidemiology to therapy, J. Thorac. Oncol. 10 (8) (2015) 1133–1141.
[2] W.D. Travis, et al., The 2015 World Health Organization Classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 classification, J. Thorac. Oncol. 10 (9) (2015) 1243–1260.
[3] N. Tsoukalas, et al., Advances on systemic treatment for lung neuroendocrine neoplasms, Ann. Transl. Med. 6 (8) (2018) 146.
[4] F.G. Fernandez, R.J. Battafarano, Large-cell neuroendocrine carcinoma of the lung: an aggressive neuroendocrine lung cancer, Semin. Thorac. Cardiovasc. Surg. 18 (3) (2006) 206–210.
[5] J. Sánchez de Cos Escuín, Diagnosis and treatment of neuroendocrine lung tumors, Arch. Bronconeumol. 50 (9) (2014) 392–396.
[6] R.J. Battafarano, et al., Large cell neuroendocrine carcinoma: an aggressive form of non-small cell lung cancer, J. Thorac. Cardiovasc. Surg. 130 (1) (2005) 166–172.
[7] M. Yoshimura, et al., Molecular Pathology of pulmonary large cell neuroendocrine carcinoma: novel concepts and treatments, Front. Oncol. 11 (2021) 671799.
[8] G.A. Masters, et al., Systemic therapy for stage IV non-small-cell lung cancer: American society of clinical oncology clinical practice guideline update, J. Clin. Oncol. 33 (30) (2015) 3488–3515.
[9] J.L. Derks, et al., Molecular subtypes of pulmonary large-cell neuroendocrine carcinoma predict chemotherapy treatment outcome, Clin. Cancer Res. 24 (1) (2018) 33–42.
[10] J. Li, et al., Prognostic value of pretreatment albumin to globulin ratio in lung cancer: a meta-analysis, Nutr. Cancer 73 (1) (2021) 75–82.
[11] T.H. Nøst, et al., Systemic inflammation markers and cancer incidence in the UK Biobank, Eur. J. Epidemiol. 36 (8) (2021) 841–848.
[12] A. Frey, et al., C-reactive protein to albumin ratio as prognostic marker in locally advanced non-small cell lung cancer treated with chemoradiotherapy, Biomedicines 10 (3) (2022).
[13] X. Guo, et al., Relationship and prognostic significance between preoperative serum albumin to globulin ratio and CT features of non-small cell lung cancer, Eur. J. Radiol. 128 (2020) 109039.
[14] Y. Chen, et al., Prognostic significance of combined preoperative platelet-to-lymphocyte ratio and lymphocyte-to-monocyte ratio in patients undergoing surgery with stage IB non-small-cell lung cancer, Cancer Manag. Res. 10 (2018) 5411–5422.
[15] Y. Wang, et al., The prognostic value of modified Glasgow prognostic score in patients with esophageal squamous cell cancer: a Meta-analysis, Nutr. Cancer 72 (7) (2020) 1146–1154.
[16] K. Watanabe, H. Masuda, D. Noma, Anesthetic and analgesic techniques and perioperative inflammation may affect the timing of recurrence after complete resection for non-small-cell lung cancer, Front Surg 9 (2022) 886241.
[17] D. Nie, et al., A high Glasgow prognostic score (GPS) or modified Glasgow prognostic score (mGPS) predicts poor prognosis in gynecologic cancers: a systematic review and meta-analysis, Arch. Gynecol. Obstet. 301 (6) (2020) 1543–1551.
[18] T. Tong, et al., A meta-analysis of glasgow prognostic score and modified glasgow prognostic score as biomarkers for predicting survival outcome in renal cell carcinoma, Front. Oncol. 10 (2020) 1541.
[19] Y. Jiang, et al., Inflammation and nutrition-based biomarkers in the prognosis of oesophageal cancer: a systematic review and meta-analysis, BMJ Open 11 (9) (2021) e048324.
[20] D. Wu, et al., Prognostic and clinical significance of modified glasgow prognostic score in pancreatic cancer: a meta-analysis of 4,629 patients, Aging (Albany NY) 13 (1) (2021) 1410–1421.
[21] P. Goldstraw, et al., The IASLC lung cancer staging Project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer, J. Thorac. Oncol. 11 (1) (2016) 39–51.
[22] K. Hiroshima, M. Mino-Kenudson, Update on large cell neuroendocrine carcinoma, Transl. Lung Cancer Res. 6 (5) (2017) 530–539.
[23] G. Veronesi, et al., Large cell neuroendocrine carcinoma of the lung: a retrospective analysis of 144 surgical cases, Lung Cancer 53 (1) (2006) 111–115.
[24] H. Kenmotsu, et al., Randomized phase III study of irinotecan plus cisplatin versus etoposide plus cisplatin for completely resected high-grade neuroendocrine carcinoma of the lung: jcog1205/1206, J. Clin. Oncol. 38 (36) (2020) 4292–4301.
[25] H. Chen, et al., Modified Glasgow prognostic score might be a prognostic factor for hepatocellular carcinoma: a meta-analysis, Panminerva Med. 59 (4) (2017) 302–307.

[26] Y. Zhang, et al., A comprehensive analysis of Glasgow Prognostic Score (GPS)/the modified Glasgow Prognostic Score (mGPS) on immune checkpoint inhibitor efficacy among patients with advanced cancer, Cancer Med. 12 (1) (2023) 38–48.
[27] J. Jin, et al., Clinical utility of the modified Glasgow prognostic score in lung cancer: a meta-analysis, PLoS One 12 (9) (2017) e0184412.
[28] M. Okui, et al., Prognostic significance of neutrophil–lymphocyte ratios in large cell neuroendocrine carcinoma, General Thoracic and Cardiovascular Surgery 65 (11) (2017) 633–639.
[29] M. Shi, et al., Neutrophil or platelet-to-lymphocyte ratios in blood are associated with poor prognosis of pulmonary large cell neuroendocrine carcinoma, Transl. Lung Cancer Res. 9 (1) (2020) 45–54.
[30] D. Fisch, et al., Comprehensive dissection of treatment patterns and outcome for patients with metastatic large-cell neuroendocrine lung carcinoma, Front. Oncol. 11 (2021) 673901.
[31] F.R. Greten, S.I. Grivennikov, Inflammation and cancer: triggers, mechanisms, and consequences, Immunity 51 (1) (2019) 27–41.