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ORIGINAL ARTICLE

Assessment of systematic inflammatory and nutritional indexes in extensive-stage small-cell lung cancer treated with first-line chemotherapy and atezolizumab

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Abstract

Background The present study aims to investigate the prognostic role of systematic inflammatory and nutritional indexes in extensive-stage small-cell lung cancer (ES-SCLC) treated with first-line chemotherapy and atezolizumab.

Materials and methods Prospective cohort population involving 53 patients were identified from NCT03041311 trial. The following peripheral blood-derived inflammatory and nutritional indexes, including neutrophil–lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), lymphocyte–monocyte ratio (LMR), systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), prognostic nutrition index (PNI), advanced lung cancer inflammation index (ALI), and lung immune prognostic index (LIPI) were evaluated.

Results The optimal cut-off values of the ALI, LMR, NLR, PLR, PNI, SII and SIRI were 323.23, 2.73, 2.57, 119.23, 48, 533.28 and 2.32, respectively. With a median follow-up of 17.1 months, the 1-year OS and PFS were 56% and 8%, respectively. Multivariate analysis showed that PLR was the only independent prognostic factors for OS among ES-SCLC patients treated with chemotherapy and atezolizumab (HR 4.63, 95%CI: 1.00–21.46, $p=0.05$). K-M analysis showed that the OS and PFS for patients with high PLR (> 119.23) were significantly poorer than these with low PLR (≤ 119.23) ($p=0.0004$ for OS and $p=0.014$ for PFS). In external validation set, prognosis of patients with high PLR was also significantly poorer than these with low PLR in terms of OS ($p=0.038$) and PFS ($p=0.028$).

Conclusion Pre-treatment PLR could serve as a valuable independent prognostic factor for ES-SCLC who receive chemotherapy and immune checkpoint inhibitors. Further, prospective studies are still needed to confirm our findings.

Keywords Small-cell lung cancer · Platelet lymphocyte ratio · Atezolizumab · Prognosis

Introduction

Lung cancer is the most commonly diagnosed cancer worldwide and the leading cause of cancer-related deaths, with 2.1 million new lung cancer cases and 1.8 million deaths predicted in 2018 [1]. Among them, small-cell lung cancer (SCLC) represents 15% of all lung cases. In general, SCLC is a highly aggressive and fatal disease, which is characterized by rapid tumor growth and early distant metastasis [2, 3]. Prior to the era of immunotherapy, limited improvements have been achieved in the treatment of SCLC, and the standard first-line treatment for extensive-stage(ES)-SCLC remains platinum-based doublet chemotherapy [4, 5]. In addition, early detection of SCLC is very challenging due to lack of specific symptoms. Therefore, approximately 70% of cases present with ES- SCLC at diagnosis [6]. The prognosis of ES-SCLC is very poor, with 5-year survival of 1–2% [7]. Therefore, novel treatment strategy for ES-SCLC is urgently needed.

As we all known, SCLC is characterized by multiple genetic alterations, reflecting its genomic instability [8]. Therefore, SCLC could be an candidate for immunotherapy by triggering an adaptive immune response that is capable of

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detecting and eradicating tumor cells. Indeed, several clinical trials have been performed to investigate the efficacy and toxicity of combining chemotherapy with immunotherapies, including anti-CTLA4, anti-PD-1 or anti-PD-L1, for the treatment of ES-SCLC [9–11]. Excepting for anti-CTLA4, adding immune checkpoint inhibitors (ICIs) to standard first-line chemotherapy provided a better survival benefit for newly diagnosed ES-SCLC. A more recent meta-analysis also showed that chemotherapy plus nivolumab, atezolizumab or durvalumab had significantly improved patient outcomes in terms of OS (hazard ratio HR, 0.67; 95% CI: 0.46–0.98 for nivolumab, HR, 0.70, 95%CI: 0.54–0.91 for atezolizumab, HR0.73; 95%CI: 0.59–0.90 for durvalumab), but not for pembrolizumab or ipilimumab [12]. Based on these findings, ICIs [13] have been approved by the US FDA as first-line and third-line settings for patients with extensive-stage or relapsed small-cell lung cancer (SCLC), respectively.

Generally, although most of ES-SCLC could benefit from ICIs, a number of patients may not respond to ICIs therapy and exhibit a shorter lifetime with ICIs treatment or suffer major life-threatening immunotoxicities [14]. In addition, the American Joint Committee on cancer tumor-node-metastasis (TNM) classification and staging system is a significant prognostic factor for SCLC patients, but it could not further stratify the same TNM stage SCLC patients with a high risk of recurrence. Therefore, it is crucial to identify effective prognostic factors to predict prognosis and to precisely stratify ES-SCLC who might benefit from chemo-immunotherapy. Systemic inflammation plays an important role in tumor promotion and progression. Therefore, it is not surprising that different markers of systemic inflammation have been related to poor outcome in multiple solid neoplasms, including SCLC. Recently, a variety of novel parameters have emerged as independent prognostic factors with an interesting role in clinical practice such as advanced lung cancer inflammation index (ALI) [15, 16], neutrophil–lymphocyte ratio (NLR) [17–19], platelet lymphocyte ratio (PLR) [17], lymphocyte–monocyte ratio (LMR) [20], systemic immune-inflammation index (SII) [21, 22], systemic inflammation response index (SIRI) [23–25], prognostic nutrition index (PNI) [26, 27], and lung immune prognostic index (LIPI) [28–30]. However, the prognosis of these inflammatory and nutritional indexes in ES-SCLC treated with chemotherapy and immunotherapy remains undetermined. As a result, we perform the present study to investigate prognostic role of systematic inflammatory and nutritional indexes in extensive-stage small-cell lung cancer (ES-SCLC) treated with first-line chemotherapy and atezolizumab.

Materials and methods

About PDS and study cohorts

Individual patient-level data were obtained from project data sphere, which was an independent, not-for-profit data-sharing platform (https://www.projectdatasphere.org/). In the present study, we used the raw individual data from one phase II randomized trial evaluating efficacy and toxicities of platinum plus etoposide chemotherapy and atezolizumab with or without trilaciclib for ES-SCLC patients (NCT03041311). The primary results of the trial were analyzed and published [31]. Patients were ineligible for inclusion if they presented with symptomatic brain metastases or had received prior systemic therapy for limited-stage or ES-SCLC. (The detailed inclusion and exclusion criteria had been presented in supplemental 1) Finally, a total of 53 patients with ES-SCLC in the controlled group treated with platinum plus etoposide chemotherapy and atezolizumab were included for analysis. In addition, a total of 31 ES-SCLC patients treated with chemotherapy and immunotherapy were used as a externally validated cohort in the present study.

Data collection

The available data of the phase II trial contain data about age at diagnosis, baseline ECOG performance status, sex, race, baseline neutrophil, lymphocytes, monocytes, platelets and leukocytes, baseline lactate dehydrogenase(LDH), albumin (g/L), baseline weight and height and smoking history. Moreover, data about progression-free survival (PFS) status and overall survival (OS) status were recorded. Based on the inclusion criteria for clinical trials, all included patients in the present study should have adequate organ function and acceptable performance status.

Definition of inflammatory markers

All hematological examinations were tested before chemotherapy and atezolizumab. Inflammatory markers were defined as follows: NLR = (the ratio of neutrophil count to lymphocyte count); LMR = (the ratio of lymphocyte count to monocyte count); PLR = (the ratio of platelet count to lymphocyte count); The PNI was the sum of albumin value (g/L) and 5 times lymphocyte count (10^9/L)[32]; SII = (platelet count) × NLR; SIRI = neutrophils × monocytes/lymphocytes[33]; ALI, advanced lung cancer inflammation index = BMI × (Albumin/NLR), BMI is the weight(kg)/height(m)^2, and NLR is the ratio of neutrophil count to lymphocyte count [33]. The LIPI composite scores were

calculated based on the dNLR (absolute neutrophil count/[white blood cell count—absolute neutrophil count]) and the baseline LDH level according to Mezquita et al. report[28]. The ALI,PLR, LMR, PLR, PNI,SII and SIRI cut-offs were utilized to select the optimal cut-off value using the receiver operating characteristic curve (ROC).

Statistical consideration

The baseline characteristics of included patients were simply described by using frequencies and percentages. Univariate and multivariate Cox-regression analyses were performed to investigate predictors for overall survival and progression-free survival. Factors significantly associated with risk of OS and PFS in the univariate analysis ($p < 0.055$) were then included for analysis in the multivariate Cox-regression analysis. OS and PFS were assessed according to PLR through Kaplan–Meier analysis. A two-tailed p value < 0.05 was considered statistically significant. Statistical analyses were conducted through NCSS version 11.0 statistical software.

Results

Patients characteristics

Baseline characteristics of the included 53 patients are shown in Table 1. All of the chemotherapy-naïve ES-SCLC patients received platinum plus etoposide chemotherapy and atezolizumab. Of them, 27 (50.9%) patients aged less than 65, while 26 (49.1%) patients older than 65; among these patients, and 46 (86.8%) had performance status of 1 or less. 34 were male and 19 were female patients; In addition, 14 patients presented with brain metastasis at initial diagnosis. As for smoking histology, 35 patients had never or former smoking status, while 18 patients were currently smoking (Table 1).

Table 1 Baseline characteristics of included 53 patients

Characteristics	N	%
Age		
< 65 years	27	50.9
≥ 65 years	26	49.1
Gender		
Male	34	64.2
Female	19	35.8
Brain metastasis at diagnosis		
Yes	14	26.4
No	39	73.6
Race		
Caucasian	51	96.2
Non-Caucasian	2	3.8
ECOG status		
0–1	46	86.8
2	7	13.2
Smoking status		
Never or former	35	66.0
Current	18	44.0
Baseline index		
PNI, median (range)	48.69 (36–60.54)	
NLR, median (range)	3.28 (1.09–15.6)	
PLR, median (range)	152.2 (48.8–680)	
LMR, median (range)	2.72 (0.75–20)	
ALI, median (range)	296.37 (64.64–1048.48)	
SII, median (range)	900.6 (155.25–5304)	
SIRI, median (range)	2.04 (0.13–9.25)	

N number, *PNI* prognostic nutrition index, *SIRI* systemic inflammation response index, *NLR* neutrophil-to-lymphocyte ratio, *LMR* lymphocyte to monocyte ratio, *PLR*, platelet to lymphocyte ratio, *SII* systemic immune-inflammation index, *ALI* advanced lung cancer inflammation index

Optimal cut-off analysis

We performed ROC curve analysis to evaluate the predictive capability of these inflammatory response markers for OS. The optimal cut-off values of the ALI, LMR, NLR, PLR, PNI, SII and SIRI were 323.23, 2.73, 2.57, 119.23, 48, 533.28 and 2.32 based on the maximum principle of the Youden index, respectively (Fig. 1).

Cox regression analysis for factors associated with OS

Data regarding age, race, BM at diagnosis, ECOG status, smoking status, NLR, PLR, LMR, SII, SIRI, PNI, ALI and LIPI score were included in univariate Cox regression analysis (Table 2). Our results indicated that ECOG status (HR 2.06 and 3.09, $p = 0.12$ and $p = 0.054$, respectively), NLR (HR 3.19, $p = 0.01$), PLR (HR 4.83, $p = 0.0012$), LMR (HR 0.44, $p = 0.023$), SII (HR 3.18, $p = 0.03$); PNI (HR 0.38, $p = 0.0055$) and LIPI (HR 1.50 and 3.43, $p = 0.37$ and $p = 0.054$, respectively) were significantly related to OS of ES-SCLC. Given the limitations of univariate analysis, multivariable Cox analysis was performed to investigate the independent factors associated with OS (Table 2). Our findings showed that PLR (HR 4.63, $p = 0.05$, Table 2) was the only independent predictor for OS among ES-SCLC treated with chemotherapy and atezolizumab.

Survival analysis according to PLR

With a median follow-up of 17.1 months (range 0.33–21.67 months), the 1-year OS was 56% and the 6-months PFS was 30%. We also performed Kaplan–Meier

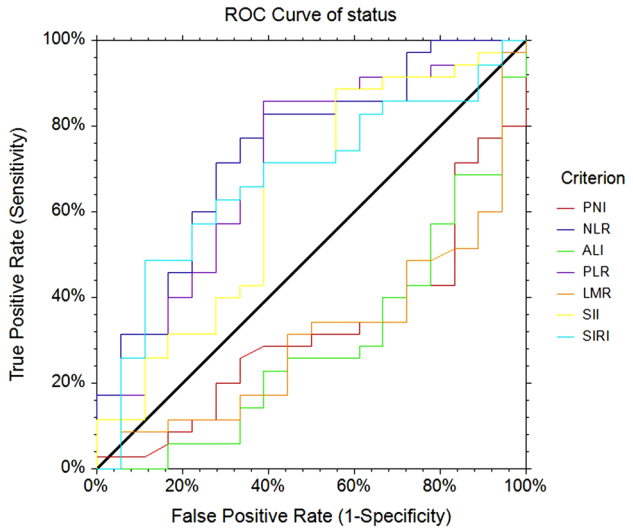

Fig. 1 ROC curve of the preoperative inflammation markers for OS. OS = overall survival, ROC = receiver operating characteristic

analysis according to baseline PLR status. Our results showed that the OS and PFS of ES-SCLC with low PLR value (≤ 119.23) were significantly higher than these with high PLR value (1-year OS: 87% vs 42%, $p = 0.0004$ Fig. 2; 6 months PFS: 50% vs. 22%, $p = 0.014$, Fig. 3).

Role of PLR in external validation set

The prognostic role of PLR was externally validated in an independent cohort of 31 ES-SCLC treated with chemotherapy and immune checkpoint inhibitors (ICIs) from our institute between November 2015 and September 2020. Of them, 20 patients treated with first-line chemotherapy and ICIs, and the other 11 patients treated with second- or third-line chemotherapy and ICIs. Until the last followed-up in January 2021, six patients had died. In consistent with our previous findings, our results also showed that prognosis of patients with high PLR was also significantly poorer than these with low PLR in terms of OS ($p = 0.038$, Fig. 3) and PFS ($p = 0.028$, Fig. 4).

Discussion

During the past decade, the introduction of ICIs for the treatment of cancer has significantly changed the clinical treatment practice of solid tumors, including SCLC. ICIs constitute a novel class of agents that block inhibitory receptors and thus harness the immune system to mount effective antitumor responses. Atezolizumab is a humanized, engineered monoclonal antibody that targeting PD-1/PD-L1 pathways. The IMpower133 study [9], a randomized

Table 2 Univariate and multivariate analysis of factors associated with OS for ES-SCLC treated with chemotherapy and atezolizumab

Factors	Univariate analysis		Multivariate analysis	
	HR, 95%CI	*P* value	HR, 95%CI	*P* value
Age				
< 65 years	1		–	
≥ 65 years	1.60 (0.82–3.13)	0.17	–	–
Gender				
Male	1		–	
Female	1.08(0.54–2.14)	0.83	–	–
BM at diagnosis				
No	1		–	
Yes	1.08 (0.54–2.15)	0.83	–	–
ECOG status				
0	1		1	
1	2.06(0.84–5.06)	0.12	1.77 (0.63–4.95)	0.27
2	3.09(0.98–9.71)	0.054	2.29(0.64–8.19)	0.20
Smoking status				
Never or former	1		–	
Current	1.22 (0.59–2.49)	0.59	–	–
NLR				
≤ 2.57	1		1	
> 2.57	3.19(1.32–7.74)	0.01	1.46(0.24–9.04)	0.69
PLR				
≤ 119.23	1		1	
> 119.23	4.83 (1.86–12.56)	0.0012	4.63(1.00–21.46)	0.05
LMR				
≤ 2.73	1		1	
> 2.73	0.44(0.22–0.90)	0.023	0.78(0.29–2.07)	0.61
SII				
≤ 533.28	1		1	
> 533.28	3.18(1.12–9.07)	0.03	0.61(0.09–4.09)	0.61
SIRI				
≤ 2.32	1		–	
> 2.32	1.83(0.94–3.58)	0.076	–	–
PNI				
≤ 48	1		1	
> 48	0.38(0.19–0.75)	0.0055	1.13(0.38–3.36)	0.82
ALI				
≤ 323.23	1		1	

Table 2 (continued)

Factors	Univariate analysis		Multivariate analysis	
	HR, 95%CI	*P* value	HR, 95%CI	*P* value
> 323.23	0.41 (0.19–0.85)	0.016	1.43 (0.42–4.95)	0.57
LIPI				
0	1		1	
1	1.50(0.61–3.69)	0.37	0.78(0.22–2.72)	0.70
2	3.43 (1.44–8.15)	0.0054	1.53(0.37–6.36)	0.56

HR hazard ratio, *OS* overall survival, *PNI* prognostic nutrition index, *SIRI*, systemic inflammation response index, *NLR* neutrophil-to-lymphocyte ratio, *LMR*, lymphocyte to monocyte ratio, *PLR* platelet to lymphocyte ratio, *SII* systemic immune-inflammation index, *ALI* advanced lung cancer inflammation index, *LIPI* lung immune prognostic index

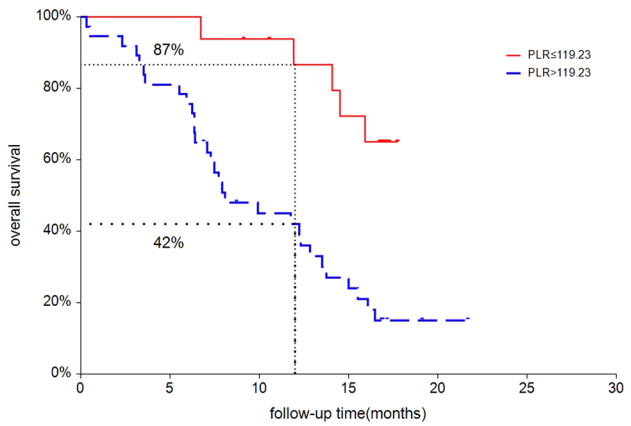

Fig. 2 Overall survival according to PLR status (≤ 119.23 vs. > 119.23)

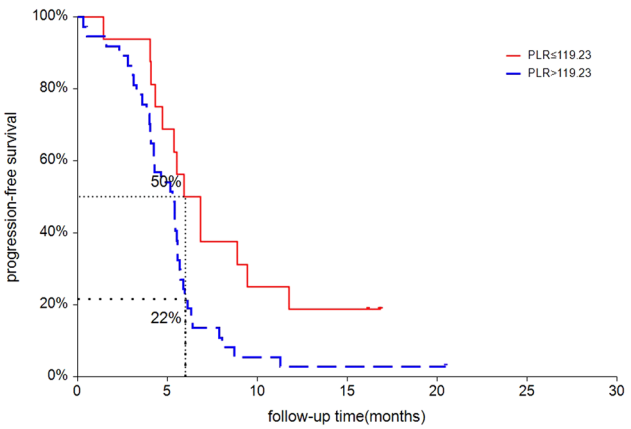

Fig. 3 Progression-free survival according to PLR status (≤ 119.23 vs. 119.23)

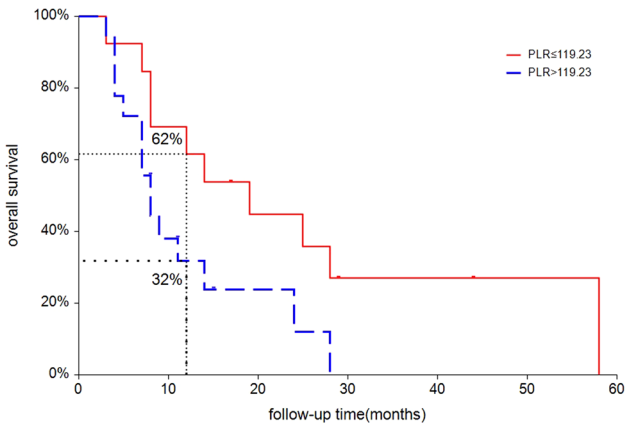

Fig. 4 Overall survival according to PLR status in external cohort

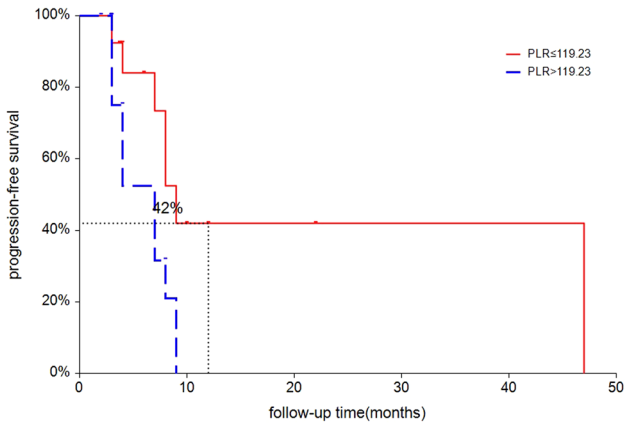

Fig. 5 Progression-free survival according to PLR status in external cohort

phase 3 trial, demonstrated that the atezolizumab combined with chemotherapy group had a median overall survival of 12.3 months, which was substantially higher than the 10.3 months observed in placebo combined chemotherapy group (HR, 0.70; 95%CI, 0.54 to 0.91; $p = 0.007$). In addition, KEYNOTE-028 study [34] also showed that the objective response rate (ORR) of pembrolizumab was 33% (95%CI: 16–55%) with acceptable toxicity profile. Therefore, it is anticipating that the usage of ICIs as a standard of care treatment for various types of cancers including SCLC could be increasing. However, the clinical benefit obtaining from ICIs therapy is not universal for all cancer patients. Therefore, it has become a priority for the oncology community to identify the optimal candidate patients for ICIs treatment by using prognostic biomarkers (Fig. 5).

Recently, increasing evidence suggests that cancer-related inflammation plays an important role in cancer development and disease progression [35]. Indeed, biomarkers of inflammation deriving from peripheral blood are significantly

associated with survival for various tumors including lung cancer [36–42]. Moreover, several inflammatory indexes, such as the NLR [43, 44], nutritional index [45], LMR [46], and LIPI [47], have also been reported as potential predictors of the effectiveness of anti-PD-1 antibody therapy. However, the prognostic of inflammatory and nutritional indexes in ES-SCLC treated with ICIs remains unknown. To our best knowledge, our study is the first to comprehensively investigate the prognostic role of systematic inflammatory and nutritional indexes in ES-SCLC treated with ICIs. Our results showed that baseline ECOG status, NLR, PLR, LMR, SII, PNI and LIPI are significantly related to OS of ES-SCLC. In the multivariate analysis, PLR is the only independent predictors for OS of ES-SCLC patients who treated with chemotherapy and atezolizumab. Additionally, an externally validation of an independent cohort of 31 patients from our institute also demonstrates that baseline PLR value is a prognostic factor for ES-SCLC treated with chemotherapy and ICIs. Prior to the present study, multiple retrospective studies, mainly focusing on non-small-cell lung cancer, have been conducted to investigate the prognostic role of PLR in cancer patients treated with immunotherapy. Bilen M. et al. [48] found that baseline and early changes in PLR were strongly associated with clinical outcomes in cancer patients immunotherapy. Subsequently, Diem S. et al. demonstrated that elevated pre-treatment NLR and PLR were significantly associated with shorter OS and PFS in NSCLC treated with nivolumab. In 2019, Xu. H. et al. [49]. performed a meta-analysis indicated that PLR could be a routinely potential prognostic factor for ICIs. And low PLR might be associated with better survival for cancer patients when treated with immunotherapy. More recently, a meta-analysis of 21 studies conducted by Zhang N. et al. also demonstrated that pre-treatment PLR could serve as prognostic biomarkers in NSCLC patients treated with ICIs [17]. Based on our findings from a second-analysis of prospective clinical trial, pre-treatment PLR could be considered as a supplement in distinguishing higher risk group of ES-SCLC treated with ICIs and predicting treatment outcomes.

However, there are several potential limitations of our study needed to be concerned. First of all, despite of the randomized, prospective nature of the included studies, our study is a retrospective analysis of the prospective trial and might have potentially selection bias. In addition, the patient population in the present study have adequate organ function and acceptable performance status thus could not represent the entire SCLC population. Secondly, the standard optimal cut-off value for these markers is yet to be established; some studies choose the median of each inflammatory marker as the cut-off value, while others determine the cut-off value based on previous studies. Therefore, how to identify the optimal value for grouping patients into high versus low PLR is one of the most challenging questions. The cut-off values of defining high versus low PLR ranged from 45 to 400 among published studies. In the present study, we use receiver operating characteristic curve to select the optimal cut-off. The optimal cut-off value of the PLR is 119.23.

Conclusion

In conclusion, the present study confirms that pre-treatment PLR could serve as a valuable independent prognostic factor of ES-SCLC who receiving chemotherapy combined with atezolizumab. In addition, pre-treatment PLR could assist physicians to perform an individualized therapeutic scheme to improve the unfavorable survival in advanced. However, multi-center and large clinical trials should be performed to confirm our findings.

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Declarations

Conflict of interest The author declares that they have no conflict of interest.

Ethical approval All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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