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ORIGINAL ARTICLE

Value of pretreatment serum lactate dehydrogenase as a prognostic and predictive factor for small-cell lung cancer patients treated with first-line platinum-containing chemotherapy

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Abstract

Background: The current study aimed to evaluate the serum pretreatment lactate dehydrogenase (LDH) and overall survival (OS) in small cell lung cancer (SCLC) patients who received first-line platinum-containing chemotherapy.

Methods: A total of 234 SCLC patients, who received first-line platinum-based chemotherapy between 2013 and 2018, were retrospectively analyzed. The data of hematological characteristics, age, gender, ECOG score, staging, metastatic site, smoking history, chemotherapy cycle, thoracic radiotherapy and hyponatremia were collected. Overall survival was calculated using the Kaplan-Meier method. The statistically significant factors in the univariate analysis were selected for the multivariate COX model analysis.

Results: Age, ECOG score, stage, thoracic radiotherapy, hyponatremia, liver metastasis, brain metastasis, bone metastasis, LDH, NSE and neutrophil-to-lymphocyte ratio (NLR) were closely correlated to OS in the univariate analysis. Furthermore, the multivariate analysis revealed that age (<65 years), ECOG score (<2 points), limited-stage (LD), thoracic radiotherapy and LDH <215.70 U/L were the independent prognostic factors for survival. The median OS time was worse for patients with LDH ≥215.70 U/L. In the subgroup analysis, LDH ≥215.70 U/L was significant for survival in both limited and extensive disease. Patients who achieved CR + PR in the first-line treatment had lower initial LDH levels. It was found that the pretreatment LDH increased the incidence of patients with liver metastasis.

Conclusions: Positive independent prognostic factors for SCLC patients were age < 65 years old, ECOG score < 2 points, LD-SCLC, and pretreatment LDH <215.70 U/L. These factors may be useful for stratifying patients with SCLC for treatment approaches.

Key points

Significant findings of the study: Age < 65 years old, ECOG score < 2 points, LD-SCLC, and pretreatment LDH <215.70 U/L are the positive independent prognostic factors for SCLC patients.

What this study adds: The current study provided more references for SCLC diagnosis and treatment and determined more factors for stratifying patients with SCLC for treatment approaches.

Introduction

A malignant tumor is a disease regulated by multiple factors and genes, which seriously threatens human health. Each year, new cases and death from lung cancer has remained at the top rank among malignant tumors in the world. Among these, SCLC accounts for 15%–20% of all lung cancer pathological types.[1] According to the classification of the Veterans Affairs Administration Lung Cancer Study Group (VALG), this can be classified as limited-stage small cell lung cancer (LD-SCLC) and extensive stage small cell lung cancer (ED-SCLC). SCLC has poor survival due to its aggressiveness and early hematogenous metastasis, with a five-year survival rate of <10%.[2] Currently, clinically sensitive and specific tumor markers with limited prognosis remain limited. Finding new tumor markers to better select patients who can use presently available methods (such as immunotherapy) would significantly contribute to clinical decision-making.

Studies have revealed that tumor cells have the Warburg effect. That is, under normal oxygen partial pressure conditions, tumor cells can break down glucose through glycolysis to obtain energy, and produce lactic acid.[3] The Warburg effect represents the transformation of glucose utilization through tumor cells from oxidative phosphorylation to glycolysis. This not only enhances the glycolysis, but also inhibits mitochondrial oxidative phosphorylation by converting pyruvate to lactic acid. Although glycolysis produces ATP much less efficiently than mitochondrial oxidative phosphorylation, its short pathway, which can be completed in the cytoplasm, is beneficial to the rapid demand for energy of tumor cells. In addition, glycolysis provides advantageous conditions for the survival and invasion of tumor cells. The aerobic glycolysis of tumor cells can not only metabolize more glucose, and provide a material basis for the synthesis of various biological macromolecules, but also promote the production and release of lactic acid. The formation of a local acidic microenvironment would be beneficial for the invasion and metastasis of tumor cells. The increase in activity of the pentose phosphate alternative pathway leads to the increase in production of reduced nicotinamide adenine dinucleotide phosphate (NADPH) and glutathione, and both of which can promote tumor cell resistance to oxidative killing and chemotherapy drugs.[4, 5]

LDH is an integral part of the Warburg effect, and is closely correlated to the proliferation and invasion of malignant tumors. As a critical enzyme in the glycolytic pathway, a large amount of pyruvate can be converted into lactic acid. LDH is a class of NAD-dependent kinases with three subunits: LDHA, LDHB and LDHC. Among these, the type A and B subunits can constitute five LDH isozymes (LDH1-5), while the C subunit constitutes only one LDH isoenzyme, LDH-C4. There is a difference in the ability of LDH1-LDH5 to catalyze the mutual conversion of pyruvate and lactic acid.[6] Studies have revealed that LDH5 expression is significantly elevated in tumor tissues.[7, 8] LDH-C4 is a tumor testis-associated antigen.[9] Present studies have suggested that LDH-C4 can also obtain energy by fermenting glucose, and promoting tumor cell growth and metastasis.[10] Lactate in healthy cells can enhance helper T cell function, and inhibit cytotoxic T lymphocyte (CTL) proliferation and cytokine production, leading to reduced cytotoxicity. In tumor cells, LDH-C4 is involved in high levels of glycolytic pathways. The lactic acid environment destroys the function of healthy helper T cells and cytotoxic T lymphocytes, resulting in loss of immune function.[11] LDH-C4 is polymerized by four C subunits, and has high thermal stability. Hence, this can be specifically separated from the other five isozymes. LDH-C4 may be a new target for tumor immunotherapy.[12]

The increase in LDH has been considered to be associated with poor survival and adverse reaction rates in melanoma.[13] Lung cancer,[14] breast cancer[15] and renal cell carcinoma[16] have also been found in tumor tissues with a high expression. LDH is expected to become a useful molecular marker or potential therapeutic target in the clinical diagnosis and treatment of tumors. Various present treatment strategies have attempted to target aerobic glycolysis to inhibit tumor progression. However, there are few studies on SCLC. The present study aims to determine the concentration between pretreatment serum LDH and survival in SCLC patients.

Methods

Patients

The patients were retrospectively identified from our patient database after the review and approval of the ethics committee of The Affiliated Hospital of Qingdao University. Written informed consent was obtained from all participants. The inclusion criteria were as follows: (i) Patients with SCLC newly confirmed by pathology from January 2013 to August 2018; (ii) patients with baseline data, such as whole blood cells, serum lactate dehydrogenase, D-dimer, NSE and CEA; (iii) patients with small cell lung cancer treated by surgery; (iv) patients who received first-line treatment with platinum-containing drugs: 4–6 cycles of platinum-based chemotherapy was routinely performed (patients who responded to chemotherapy received consolidation thoracic radiotherapy [TRT] in the chest, and patients with brain metastases received whole-brain radiotherapy [WBRT] before or after chemotherapy, depending on the symptom); (v) patients with adequate imaging evidence that could be used to determine the SCLC stage

before treatment; and (vi) patients with complete follow-up data. Exclusion criteria were as follows: (i) patients with composite SCLC, which contained the components of other pathological types; and (ii) patients with other blood systems and solid tumors.

Data collection

Variables including clinical characteristics and treatment characteristics were collected from the case system. From the day of diagnosis to the start of any treatment (chemotherapy or radiation therapy), the required monitoring indicators were collected in whole blood, serum blood and plasma before treatment. NLR was calculated by dividing the total neutrophil count by the lymphocyte count (TLC). Similarly, the platelet-lymphocyte ratio (PLR) was calculated by dividing the total platelet count by the TLC. The time-dependent ROC curve was then drawn based on the baseline hematological indicators (LDH, plasma D-dimer, CEA, NSE, platelets, neutrophils, TLC, NLR and PLR), the optimal cutoff value was determined, and the patients stratified. The other variable clinical features included age (<65 or ≥ 65 years old), gender, smoking history, stage, ECOG score, metastatic site (liver, brain and bone), and blood sodium status.

Statistical analysis

The clinicopathological and therapeutic characteristics were summarized through descriptive analysis. The differences between the higher-LDH (≥215.60 U/L) and lower-LDH groups were compared using a chi-square test or Mann-Whitney U test, as appropriate. The log-rank test was used to compare the Kaplan-Meier survival estimates between groups. Statistical analysis was performed using SPSS Statistics 21 (SPSS Inc., Chicago, IL, USA). The main purpose was to observe the overall survival (OS), which was calculated from the date of diagnosis to the date of death or last follow-up. With the exception of first-line treatment evaluations, all pretreatment characteristics were evaluated as covariates. A univariate proportional hazard Cox model was used to assess the potential association between these characteristics and OS. Factors with a *P*-value of <0.05 were included in the multivariate assessment. The Wald test was used to evaluate the role of covariates in the model. All statistical tests were two-sided, and a *P*-value of <0.05 was considered statistically significant.

Results

A total of 234 patients met the inclusion criteria, and were included in the present analysis (Table 1). The median age of patients was 60 years (interquartile range [IQR] 53–65). Furthermore, 54% of patients had LD-SCLC, 73% of patients had a history of smoking, 24% of patients were female, 6% of patients had an ECOG score of ≥2, and 25% had hyponatremia. In addition, 90% of patients had ≥4 cycles of platinum chemotherapy, and 57% had received consolidation or remission after TRT. ED patients (44%) with higher (≥215.70 U/L) preconditioning LDH were greater than patients with LD (31%) (P = 0.033). Furthermore, there were more patients with liver metastases (64%) with higher pretreatment of LDH, when compared to patients without liver metastases (51%) (*P* = 0.033). The pretreatment platelet, neutrophil, D-dimer and NSE counts were generally lower in patients who had low LDH. For the treatment details, 134 patients (63%) received TRT, 120 (45%) patients received ≥45 Gy, and 14 (6%) patients received <45 Gy. TRT was used for 34 patients for palliative or salvage, while 100 patients did not receive TRT. As for the chemotherapy, merely 23 patients received 1–3 cycles of chemotherapy, while 211 patients received ≥4 cycles (Table 1).

The median OS time for all patients was 18.7 months (95% CI: 16.4–21.0). The median OS time was 21.3 months (95% CI: 17.6–25.0) for patients with pretreatment LDH ≥215.70 U/L versus 16.1 months (95% CI: 14.2–18.0) for patients with pretreatment LDH <215.70 U/L (log-rank $P < 0.001$, Fig 1a). The one-year survival rates were 77.6% and 67.8%, respectively, the two-year survival rates were 42.7% and 20.9%, respectively, and the three-year survival rates were 17.9% and 4.0%, respectively. After grouping by stage, it was found that without the limitation of the stage, LDH has significance for predicting patients with LD and ED SCLC. The median OS time for LD patients was 22.7 months (95% CI: 20.5–24.9). The median OS was 23.5 months for LD patients with pretreated LDH <215.70 U/L (95% CI: 21.0–26.1), and 21.0 months for patients with pretreated LDH ≥215.70 U/L (95% CI: 16.2–25.7) (log-rank $P = 0.049$, Fig 1b). The median OS time for ED patients was 13.0 months (95% CI: 11.1–15.0). The median OS was 15.2 months for ED patients with pretreated LDH < 215.70 U/L (95% CI: 11.7–18.7), and 12.3 months for ED patients with pretreated LDH ≥ 215.70 U/L (95% CI: 10.8–13.7) (log rank $P = 0.028$, Fig 1c).

A total of 12 survival-related factors were identified in the univariate analysis: age, gender, ECOG score, staging, metastasis in the liver, bone, or brain, thoracic radiotherapy, LDH, TLC, NLR and NSE ($P < 0.05$). However, no significant differences were observed in survival, based on hyponatremia and smoking status. Furthermore, there was no significant correlation among PLR pretreatment, CEA, d-dimer count, lymphocyte count, platelet count and survival time (Table 2).

Table 1 Patient characteristics

Characteristic	All Patients (n = 234)	Patients with LDH <217 U/L (%)	Patients with LDH ≥217 U/L (%)	P-value
No. of patients (%)	234 (100)	147 (63)	87 (37)	
Age at diagnosis, years, median (IQR)	60 (53–66)	60 (51–65)	60 (56–66)	0.472
Gender				0.313
Male	178 (76)	115 (78)	63 (72)	
Female	56 (24)	32 (22)	24 (28)	
ECOG PS				0.572
0–1	219 (94)	139 (95)	80 (92)	
≥2	15 (6)	8 (5)	7 (8)	
Smoking status				0.706
Yes	173 (74)	109 (74)	64 (73)	
No	61 (26)	38 (26)	23 (27)	
Stage				0.033
LS-SCLC	126 (54)	87 (59)	39 (45)	
ES-SCLC	108 (46)	60 (41)	48 (55)	
Metastasis to liver				0.003
Yes	25 (11)	9 (6)	16 (18)	
No	209 (89)	138 (94)	71 (82)	
Metastasis to brain				0.75
Yes	15 (6)	10 (7)	5 (6)	
No	219 (94)	137 (93)	82 (94)	
Metastasis to bone				0.069
Yes	25 (10)	11 (8)	13 (15)	
No	210 (90)	136 (92)	74 (85)	
No. of chemotherapy cycles				0.838
<4	23 (10)	14 (10)	9 (10)	
≥4	211 (90)	133 (90)	78 (90)	
Receipt of thoracic RT				0.822
Yes	134 (57)	85 (58)	49 (56)	
No	100 (42)	62 (42)	38 (44)	
First-line treatment evaluation				0.05
CR + PR	153 (65)	44 (30)	37 (42)	
SD + PD	81 (35)	103 (70)	50 (58)	
Hyponatremia				0.282
Yes	58 (25)	33 (78)	25 (29)	
No	176 (75)	114 (22)	62 (71)	
Median platelets $\times 10^9$/L (IQR)	239 (205–303)	235 (194–293)	250 (214–333)	0.03
Median neutrophils $\times 10^9$/L (IQR)	4.3 (3.3–5.2)	4.1 (3.1–5.1)	4.6 (3.6–5.6)	0.036
Median TLC $\times 10^9$/L (IQR)	1.8 (1.3–2.2)	1.7 (1.3–2.2)	1.8 (1.1–2.2)	0.512
Median NLR (IQR)	2.5 (1.7–3.5)	2.4 (1.6–3.3)	2.5 (1.9–4.0)	0.072
Median PLR (IQR)	143.7 (105.8–196.2)	140.0 (98.0–193.7)	150.0 (112.6–217.7)	0.054
Median LDH, U/L (IQR)	189.5 (157.5–238.1)	166.0 (142.0–186.0)	254.0 (230.0–308.5)	0.001
Median D-dimer, ng/mL (IQR)	460.0 (260.0–653.0)	230.0 (390.0–606.0)	606.0 (300.0–800.0)	<0.001
Median CEA, ng/mL (IQR)	3.7 (2.3–8.3)	3.5 (2.2–5.9)	5.0 (2.4–13.4)	0.091
Median NSE, ng/mL (IQR)	47.0 (26.7–80.3)	40.7 (21.4–66.6)	66.6 (45.0–126.9)	<0.001

IQR, interquartile range; ECOG PS, Eastern Cooperative Oncology Group performance status; RT, radiation therapy; TLC, total lymphocyte count; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LDH, lactate dehydrogenase; CEA, carcinoembryonic antigen; NSE, neuron-specific enolase.

The final multivariate analysis revealed that high pre-treatment LDH (HR: 1.468, 95% CI: 1.069–2.017, P = 0.018) was an independent predictor of decreased survival. In the multivariate analysis, four other clinicopathological features (age ≥ 65, ECOG score ≥ 2, no thoracic radiotherapy, and extensive phase) were also identified as independent predictors of OS deterioration ($P < 0.05$) (Table 3).

Although the NSE count ≥40.80 ng/mL and NLR ≥4.8 in the univariate analysis were better correlated with prognosis (HR: 1.413, 95% CI: 1.022–1.954, P = 0.011, HR: 1.418, 95% CI: 1.089–1.924, P = 0.037), this apparent

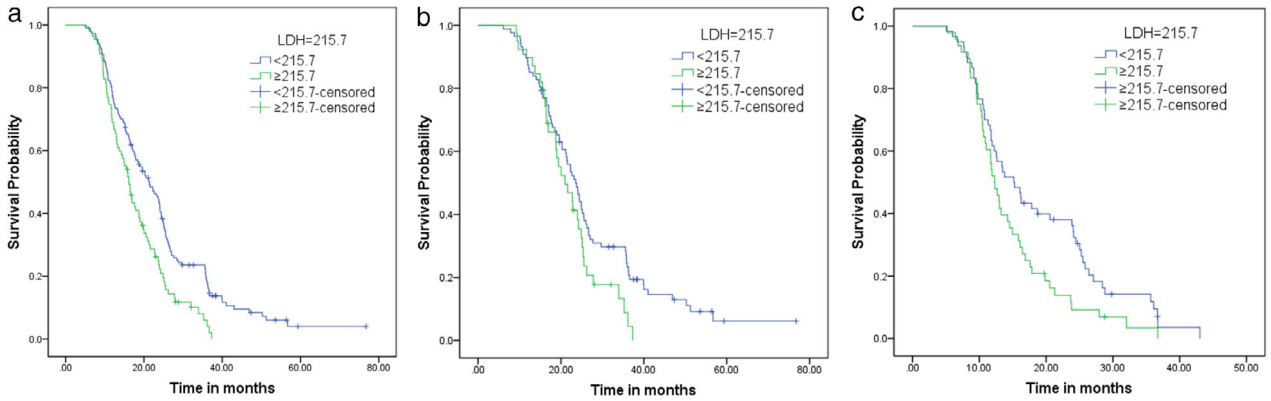

Figure 1 The Kaplan-Meier plot for survival stratified by pretreatment LDH level in (**a**) all SCLC patients (——) <215.7, (——) ≥215.7, (—+—) <215.7-censored, (—+—) ≥215.7-censored; (**b**) LD-SCLC patients (——) <215.7, (——) ≥215.7, (—+—) <215.7-censored, (—+—) ≥215.7-censored; (**c**) ED-SCLC patients (——) <215.7, (——) ≥215.7, (—+—) ≥215.7-censored, (—+—) ≥215.7-censored.

association did not hold in the multivariate analysis (Tables 2 and 3).

Discussion

Previous studies have indicated that age, ECOG score, staging and thoracic radiotherapy are independently correlated to the OS of SCLC,[17, 18] and the present study also reached the same conclusion. The data obtained from the present study indicates that age ≥ 65 years old, ECOG score < 2 points, localized, and first-line thoracic radiotherapy were independent favorable prognostic factors for survival in SCLC, based on the platinum chemotherapy. The present study also implies that pretreatment serum LDH ≥215.70 U/L is significantly correlated to prognosis. Hence, the correlation of pre-treated LDH mentioned in previous studies has been confirmed.

LDH has been widely investigated as a prognostic indicator in various malignancies, including lung cancer.[19–22] The most recent LDH and SCLC studies have suggested that high LDH levels indicate worse results. The findings reported by Sagman *et al.*[23] included 288 SCLC patients, and it was established that serum LDH appears to be a significant independent pretreatment prognostic factor for patients with SCLC, which correlates with the stage of the disease, response to treatment, and survival. The median for patients with elevated LDH was 39 weeks, while for patients with low LDH levels, the median was 53 weeks. The incidence of abnormal increase in LDH in ED patients was significantly higher, when compared to LD patients. The subgroup analysis revealed that the CR rates were inversely proportional to the LDH levels in LD patients ($P = 0.026$), and that patients with elevated LDH levels had higher mortality rates (1.63:1.00), which was not the same for ED patients. Lassen *et al.*[24] investigated 484 patients who underwent first-line chemotherapy, and multivariate analysis revealed that in addition to the presence or absence of platinum-induced chemotherapy as an independent risk factor for survival, elevated LDH was also an independent factor for prognosis. The study conducted by Zhou *et al.*[25] revealed that a relatively short survival time ($P = 0.008$) was predicted in patients with elevated LDHs, and that patients with elevated LDHs had a 1.41 times higher risk of death, when compared to the normal group. When these were stratified by stage, there was a significant correlation between LDH levels and OS in ED patients ($P = 0.003$), but there was no statistical significance in patients with localized stages. However, the study conducted in South Korea by Jong *et al.*[26] indicated that LDH is not an independent prognostic factor for SCLC.

It has been hypothesized that LDH has a prognostic value, and can better predict the overall survival of SCLC patients. The multivariate analysis indicated that there was a significant difference in survival between patients with LDH ≥215.70 U/L and patients with LDH <215.70 U/L ($P = 0.018$), with a median OS of 21.279 months and 16.131 months, respectively. Patients with elevated LDH (≥215.70 U/L) had a 1.459-fold higher risk of death, when compared to patients with low LDH (95% CI: 1.054–2.020). The one-, two- and three-year survival rates in the low LDH group were better, when compared to the high LDH group. The subgroup analysis indicated that regardless of the stage, LDH ≥215.70 suggests a poor prognosis in both LD and ED patients ($P = 0.049$, $P = 0{,}028$), and that the difference was more pronounced in patients with extensive stages.

In the present retrospective study, the relationship between LDH levels and treatment response was analyzed. The study conducted by Wen *et al.*[27] indicated that LDH levels could not independently predict whether patients with SCLC are platinum-sensitive, but LDH was an independent prognostic factor for OS. These present findings

Table 2 Univariate analysis of factors potentially associated with overall survival

Variable	Hazard ratio	95% CI	*P*-value
Age		1.009–1.868	0.044
<65	1		
≥65	1.373		
Gender		1.017–1.955	0.04
Female	1		
Male	1.41		
ECOG PS		1.175–3.404	0.011
0–1	1		
≥2	2		
Smoking status		0.944–1.763	0.111
No	1		
Yes	1.29		
Stage		1.555–2.714	<0.001
LS-SCLC	1		
ES-SCLC	2.055		
Metastasis to liver		1.863–4.367	<0.001
No	1		
Yes	2.852		
Metastasis to brain		1.322–4.150	0.004
No	1		
Yes	2.343		
Metastasis to bone		1.571–3.739	<0.001
No	1		
Yes	2.424		
No. of chemotherapy cycles		0.422–1.044	0.076
<4	1		
≥4	0.664		
Receipt of thoracic RT		0.419–0.732	<0.001
No	1		
Yes	0.554		
Hyponatremia		1.042–1.927	0.026
No	1		
Yes	1.417		
Pretreatment platelets		0.721–1.267	0.753
$<269 \times 10^9$/L	1		
$\geq 269 \times 10^9$/L	0.956		
Pretreatment TLC		0.647–1.141	0.295
$<2.0 \times 10^9$/L	1		
$\geq 2.0 \times 10^9$/L	0.859		
Pretreatment NLR		1.022–1.954	0.037
<3.80	1		
≥3.80	1.413		
Pretreatment PLR		0.814–1.425	0.605
<124.70	1		
≥124.70	1.077		
Pretreatment LDH		1.255–2.233	<0.001
<215.70 U/L	1		
≥215.70 U/L	1.674		
Pretreatment D-dimer		0.825–1.449	0.386
<585 ng/mL	1		
≥585 ng/mL	1.093		
Pretreatment CEA		0.973–1.688	0.078
<4.80 ng/mL	1		
≥4.80 ng/mL	1.281		
Pretreatment NSE		1.089–1.924	0.011
<40.80 ng/mL	1		
≥40.80 ng/mL	1.448		

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; RT, radiation therapy; TLC, total lymphocyte count; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LDH, lactate dehydrogenase; CEA, carcinoembryonic antigen; NSE, neuron-specific enolase.

Table 3 Multivariate analysis of factors potentially associated with overall survival

Variable	Hazard ratio	95% CI	*P*-value
Age		1.087–2.062	0.014
<65	1		
≥65	1.497		
Gender		0.888–1.751	0.203
Female	1		
Male	1.247		
ECOG		1.317–4.198	0.004
0–1	1		
≥2	2.351		
Stage		1.120–2.233	0.009
LS-SCLC	1		
ES-SCLC	1.581		
Metastasis to liver		0.825–2.296	0.221
No	1		
Yes	1.376		
Metastasis to brain		0.710–2.471	0.378
No	1		
Yes	1.324		
Metastasis to bone		0.865–2.311	0.167
No	1		
Yes	1.414		
Receipt of thoracic RT			
No	1	0.498–0.956	0.026
Yes	0.69		
Hyponatremia			
No	1	0.922–1.768	0.141
Yes	1.277		
Pretreatment NLR		0.606–1.270	0.489
<3.80	1		
≥3.80	0.878		
Pretreatment LDH		1.069–2.017	0.018
<215.70 U/L	1		
≥215.70 U/L	1.468		
Pretreatment NSE		0.898–1.709	0.191
<40.80 ng/mL	1		
≥40.80 ng/mL	1.239		

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; RT, radiation therapy; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; NSE, neuron-specific enolase.

revealed that LDH was correlated not only to survival, but also to the incidence of LDH elevations that reached CR + PR, which were lower in patients with stable and progressive disease ($P = 0.050$).

Previous studies have suggested that elevated LDH may be associated with tumor metastasis.[28, 29] Dong *et al.*[30] reported that the expression of LDH in tumor tissues and serum LDH status are closely correlated to the occurrence of brain metastases in triple-negative breast cancer, and that these were predictors of brain metastasis in triple-negative breast cancer. The study conducted by Anami *et al.*[31] implicated that the increase in LDH is associated with the occurrence and prognosis of brain metastases in SCLC patients, and that the increase in LDH in patients with brain metastases suggests a shorter survival. A Swiss study[32] demonstrated that LDH is a predictor of bone metastases in SCLC, and that the increase in LDH levels is positively correlated with the incidence of bone metastases. These above results suggest that the increase of LDH may predict the possibility of metastasis in SCLC patients. The present study demonstrated that the LDH levels of patients were correlated with the occurrence of liver metastases ($P = 0.050$). LDH levels were higher in patients with liver metastases. In the group analysis for liver, bone and brain metastasis, the worst OS was found in patients with liver metastasis, which is consistent with the results of a previous study.[33] Indeed, the link between LDH levels and the occurrence of SCLC liver metastasis still needs to be confirmed through further large-scale prospective studies.

Inflammation plays a vital role in cancer development. NLR and PLR are markers of inflammation and immune status, and these have been investigated as prognostic indicators in various malignancies.[34-37] There are also many related studies in SCLC. Suzuki *et al.*[38] conducted a study on 252 ED-SCLC patients, and revealed that the OS of patients with TLC counts $>1.5 \times 10^3/\mu L$ before treatment was significantly different, when compared to that of patients with TLC counts $<1.5 \times 10^3/\mu L$ before treatment. The OS was 12.0 months and 9.8 months ($P = 0.021$), respectively. The median OS time of patients with NLR ≥4.0 before treatment was 9.40–13.90 months ($P = 0.002$), respectively. However, there was no significant difference between PLR groups. Another study[39] revealed that TLC, NLR and PLR are independent indicators of survival in patients with LD-SCLC ($P = 0.028$, $P = 0.011$ and $P = 0.030$). The results from two other single institutions[40, 41] suggest that pretreatment NLR, rather than PLR, is an independent predictor of prognosis. However, Xie *et al.*[42] conducted separate studies on ES-SCLC and LS-SCLC, and found that NLR before treatment was only valid for ES-SCLC patients, and that PLR before treatment was only active for LS-SCLC patients. The present results revealed that there was no significant correlation between pretreatment PLR and TLC with OS. The subgroup analysis revealed that PLR was only different among patients in the extensive phase (log-rank $P = 0.048$). Furthermore, NLR was significant in the univariate analysis, while NLR was not significant in the multivariate analysis. This is different from previous research results. NLR and PLR are not specific markers of tumors, and are easily affected by radiation and inflammation. It has been confirmed that the high heterogeneity of SCLC and the difference in population selection had an impact on these results. Further studies are needed to confirm the importance of preprocessing NLR and PLR in SCLC outcomes.

There were several limitations in the present study. The present study was a single-center retrospective study. The

relatively few qualified patients limited the heterogeneity of these patients, and the impact of WBRT on the prognosis was not collected from these patients.

In conclusion, patients age < 65 years old, ECOG score < 2 points, thoracic radiotherapy, and LDH <215.70 U/L are positive independent prognostic factors for SCLC patients, based on first-line platinum-based chemotherapy. Accordingly, more extensive prospective studies are needed to confirm these results.

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Disclosure

No authors report any conflict of interest.

References

1 Stupp R, Monnerat C, Turrisi AT *et al.* Small cell lung cancer: State of the art and future perspectives. *Lung Cancer* 2004; **45**: 105–17.
2 van Meerbeeck JP, Fennell DA, De Ruysscher DK. Small-cell lung cancer. *Lancet* 2011; **378**: 1741–55.
3 Koppenol WH, Bounds PL, Dang CV. Otto Warburg's contributions to current concepts of cancer metabolism. *Nat Rev Cancer* 2011; **11**: 325–37.
4 Vander Heiden MG, Cantley LC, Thompson CB. Understanding the Warburg effect: The metabolic requirements of cell proliferation. *Science* 2009; **324**: 1029–33.
5 Kim JW, Dang CV. Cancer's molecular sweet tooth and the Warburg effect. *Cancer Res* 2006; **66**: 8927–30.
6 Feron O. Pyruvate into lactate and back: From the Warburg effect to symbiotic energy fuel exchange in cancer cells. *Radiother Oncol* 2009; **92**: 329–33.
7 Kayser G, Kassem A, Sienel W *et al.* Lactate-dehydrogenase 5 is overexpressed in non-small cell lung cancer and correlates with the expression of the transketolase-like protein 1. *Diagn Pathol* 2010; **5**: 22.
8 Koukourakis MI, Giatromanolaki A, Simopoulos C, Polychronidis A, Sivridis E. Lactate dehydrogenase 5 (LDH5) relates to up-regulated hypoxia inducible factor pathway and metastasis in colorectal cancer. *Clin Exp Metastasis* 2005; **22**: 25–30.
9 Bart J, Groen HJ, van der Graaf WT *et al.* An oncological view on the blood-testis barrier. *Lancet Oncol* 2002; **3**: 357–63.
10 Rodriguez-Paez L, Chena-Taboada MA, Cabrera-Hernandez A *et al.* Oxamic acid analogues as LDH-C4-specific competitive inhibitors. *J Enzyme Inhib Med Chem* 2011; **26**: 579–86.
11 Droge W, Roth S, Altmann A *et al.* Regulation of T-cell functions by L-lactate. *Cell Immunol* 1987; **108**: 405–16.
12 Koslowski M, Tureci O, Bell C *et al.* Multiple splice variants of lactate dehydrogenase C selectively expressed in human cancer. *Cancer Res* 2002; **62**: 6750–5.
13 Wagner NB, Forschner A, Leiter U, Garbe C, Eigentler TK. S100B and LDH as early prognostic markers for response and overall survival in melanoma patients treated with anti-PD-1 or combined anti-PD-1 plus anti-CTLA-4 antibodies. *Br J Cancer* 2018; **119**: 339–46.
14 Grunwald C, Koslowski M, Arsiray T *et al.* Expression of multiple epigenetically regulated cancer/germline genes in nonsmall cell lung cancer. *Int J Cancer* 2006; **118**: 2522–8.
15 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin* 2017; **67**: 7–30.
16 Hua Y, Liang C, Zhu J *et al.* Expression of lactate dehydrogenase C correlates with poor prognosis in renal cell carcinoma. *Tumour Biol* 2017; **39**: 1010428317695968.
17 Cao S, Jin S, Shen J *et al.* Selected patients can benefit more from the management of etoposide and platinum-based chemotherapy and thoracic irradiation-a retrospective analysis of 707 small cell lung cancer patients. *Oncotarget* 2017; **8**: 8657–69.
18 Paesmans M, Sculier JP, Lecomte J *et al.* Prognostic factors for patients with small cell lung carcinoma: Analysis of a series of 763 patients included in 4 consecutive prospective trials with a minimum follow-up of 5 years. *Cancer* 2000; **89**: 523–33.
19 Kazandjian D, Gong Y, Keegan P, Pazdur R, Blumenthal GM. Prognostic value of the lung immune prognostic index for patients treated for metastatic non-small cell lung cancer. *JAMA Oncol* 2019; **5**: 1481.
20 Pietrantonio F, Miceli R, Rimassa L *et al.* Estimating 12-week death probability in patients with refractory metastatic colorectal cancer: The colon life nomogram. *Ann Oncol* 2017; **28**: 555–61.
21 Tang LQ, Li CF, Li J *et al.* Establishment and validation of prognostic Nomograms for endemic nasopharyngeal carcinoma. *J Natl Cancer Inst* 2016; **108**: djv291.
22 Scher HI, Heller G, Molina A a. Circulating tumor cell biomarker panel as an individual-level surrogate for survival in metastatic castration-resistant prostate cancer. *J Clin Oncol* 2015; **33**: 1348–55.
23 Sagman U, Feld R, Evans WK *et al.* The prognostic significance of pretreatment serum lactate dehydrogenase in patients with small-cell lung cancer. *J Clin Oncol* 1991; **9**: 954–61.
24 Lassen U, Kristjansen PE, Osterlind K *et al.* Superiority of cisplatin or carboplatin in combination with teniposide and vincristine in the induction chemotherapy of small-cell lung cancer. A randomized trial with 5 years follow up. *Ann Oncol* 1996; **7**: 365–71.

25 Zhou T, Zhan J, Hong S *et al*. Ratio of C-reactive protein/albumin is an inflammatory prognostic score for predicting overall survival of patients with small-cell lung cancer. *Sci Rep* 2015; **5**: 10481.
26 Oh J-R, Seo J-H, Chong A *et al*. Whole-body metabolic tumour volume of 18F-FDG PET/CT improves the prediction of prognosis in small cell lung cancer. *Eur J Nucl Med Mol Imaging* 2012; **39**: 925–35.
27 Wen Q, Meng X, Xie P, Wang S, Sun X, Yu J. Evaluation of factors associated with platinum-sensitivity status and survival in limited-stage small cell lung cancer patients treated with chemoradiotherapy. *Oncotarget* 2017; **8**: 81405–18.
28 Katakami N, Kunikane H, Takeda K *et al*. Prospective study on the incidence of bone metastasis (BM) and skeletal-related events (SREs) in patients (pts) with stage IIIB and IV lung cancer-CSP-HOR 13. *J Thorac Oncol* 2014; **9**: 231–8.
29 Gershenwald JE, Scolyer RA, Hess KR *et al*. Melanoma staging: Evidence-based changes in the American joint committee on cancer eighth edition cancer staging manual. *CA Cancer J Clin* 2017; **67**: 472–92.
30 Dong T, Liu Z, Xuan Q, Wang Z, Ma W, Zhang Q. Tumor LDH-A expression and serum LDH status are two metabolic predictors for triple negative breast cancer brain metastasis. *Sci Rep* 2017; **7**: 6069.
31 Anami S, Doi H, Nakamatsu K *et al*. Serum lactate dehydrogenase predicts survival in small-cell lung cancer patients with brain metastases that were treated with whole-brain radiotherapy. *J Radiat Res* 2019; **60**: 257–63.
32 Conen K, Hagmann R, Hess V, Zippelius A, Rothschild SI. Incidence and predictors of bone metastases (BM) and skeletal-related events (SREs) in small cell lung cancer (SCLC): A Swiss patient cohort. *J Cancer* 2016; **7**: 2110–6.
33 Cai H, Wang H, Li Z, Lin J, Yu J. The prognostic analysis of different metastatic patterns in extensive-stage small-cell lung cancer patients: A large population-based study. *Future Oncol* 2018; **14**: 1397–407.
34 Yodying H, Matsuda A, Miyashita M *et al*. Prognostic significance of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in oncologic outcomes of esophageal cancer: A systematic review and meta-analysis. *Ann Surg Oncol* 2016; **23**: 646–54.
35 Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. *Nature* 2008; **454**: 436–44.
36 Shalapour S, Karin M. Immunity, inflammation, and cancer: An eternal fight between good and evil. *J Clin Invest* 2015; **125**: 3347–55.
37 Templeton AJ, Ace O, McNamara MG *et al*. Prognostic role of platelet to lymphocyte ratio in solid tumors: A systematic review and meta-analysis. *Cancer Epidemiol Biomarkers Prev* 2014; **23**: 1204–12.
38 Suzuki R, Lin SH, Wei X *et al*. Prognostic significance of pretreatment total lymphocyte count and neutrophil-to-lymphocyte ratio in extensive-stage small-cell lung cancer. *Radiother Oncol* 2018; **126**: 499–505.
39 Suzuki R, Wei X, Allen PK, Cox JD, Komaki R, Lin SH. Prognostic significance of Total lymphocyte count, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio in limited-stage small-cell lung cancer. *Clin Lung Cancer* 2019; **20**: 117–23.
40 Deng M, Ma X, Liang X, Zhu C, Wang M. Are pretreatment neutrophil-lymphocyte ratio and platelet-lymphocyte ratio useful in predicting the outcomes of patients with small-cell lung cancer? *Oncotarget* 2017; **8**: 37200–7.
41 Yi F, Gu Y, Chen S *et al*. Impact of the pretreatment or posttreatment NLR and PLR on the response of first line chemotherapy and the outcomes in patients with advanced non-small cell lung cancer. *Zhongguo Fei Ai Za Zhi* 2018; **21**: 481–92.
42 Xie D, Marks R, Zhang M *et al*. Nomograms predict overall survival for patients with small-cell lung cancer incorporating pretreatment peripheral blood markers. *J Thorac Oncol* 2015; **10**: 1213–20.

