ORIGINAL RESEARCH

Impact of inflammatory markers on survival in patients with limited disease small-cell lung cancer undergoing chemoradiotherapy

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Background: Systemic inflammation appears to play a role in the progression of numerous solid tumors by promoting tumor proliferation. Our current study aimed to evaluate the role of inflammatory markers in limited disease (LD) small-cell lung cancer (SCLC) patients undergoing thoracic chemoradiotherapy (TCR).

Patients and methods: We retrospectively analyzed a total number of 350 SCLC patients diagnosed with LD SCLC who received TCR between 1999 and 2017 and had available blood tests within 2 weeks prior to the start of TCR. Serum C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR), lactate dehydrogenase (LDH), hemoglobin (Hb) levels, and platelet count (Pc) were evaluated as potential inflammatory markers. Kaplan–Meier survival analysis was performed for overall survival (OS). For comparison of survival curves, the log-rank (Mantel–Cox) test was used. Univariate and multivariate Cox proportional HRs were used to assess the influence of cofactors on OS.

Results: Univariate analysis for OS revealed a statistically significant effect for LDH >400 U/L (HR 2.05 U/L; 95% CI 1.29–3.26 U/L; *P*=0.002), prophylactic cranial irradiation (PCI; HR 0.58; 95% CI 0.40–0.85; *P*=0.005), CRP >50 mg/L (HR 1.49 mg/L; 95% CI 1.05–2.10 mg/L; *P*=0.026), and Karnofsky performance scale (KPS) <70% (HR 1.35%; 95% CI 1.02–1.80%; *P*=0.035). NLR, age (>70 years), Hb levels, and Pc did not influence survival. In multivariate analysis, OS was significantly affected by PCI (HR 0.64; 95% CI 0.43–0.94; *P*=0.026), LDH >400 U/L (HR 1.91 U/L; 95% CI 1.21–3.05 U/L; *P*=0.006), and CRP >50 mg/L (HR 1.43 mg/L; 95% CI 1.01–2.04 mg/L; *P*=0.045). KPS (≤70%) did not influence survival in multivariate analysis.

Conclusion: Elevated CRP and LDH seem to be the independent prognostic factors for OS in LD SCLC patients undergoing TCR. However, elevated NLR was not found to be an independent prognostic factor for OS if taken prior to TCR. LDH and CRP are easily available blood tests and do not require additional resources for routine use and could be useful for clinical decision making.

Keywords: small-cell lung cancer, limited disease, comorbidity, NLR, LDH, CRP

Introduction

Systemic inflammation is increasingly being recognized as an important prognostic factor of survival in cancer patients, and several markers of systemic inflammation, such as C-reactive protein (CRP) and lactate dehydrogenase (LDH), were investigated for their potential impact on outcomes.[1–5] Furthermore, several studies suggested that neutrophil-to-lymphocyte ratio (NLR) had a prognostic value in predicting the survival of patients with solid tumors.[6–14] As nonspecific inflammatory markers, previous research found that the elevation of pretreatment NLR, LDH, and CRP was

negatively associated with survival in lung cancer patients. However, the results of individual studies are inconsistent, particularly between histological subtypes and disease stage. Currently, there are several analyses available for non-small-cell lung cancer (NSCLC) subtypes, but the data on SCLC patients are inconsistent with small cohorts, inhomogeneous treatments, or mixed disease stage.[7–9,12,14–18] Moreover, NLR cutoff values are yet determined to be safely used for clinical decision making.

This study assessed the prognostic value of the pretreatment inflammatory markers in limited disease (LD) SCLC patients undergoing thoracic chemoradiotherapy (TCR).

Patients and methods
Patients and treatment features

We identified 350 patients in our cancer center database who had histologically confirmed LD SCLC according to the classification of the Veterans Affairs Administration Lung Cancer Study Group (VALG)[19] between 1999 and 2017, which received standard concurrent TCR as a first-line treatment. Blood tests within 2 weeks prior to the start of TCR were retrospectively used for analysis. Serum CRP, NLR, LDH, hemoglobin (Hb) levels, and platelet count (Pc) were evaluated as potential inflammatory markers. Thoracic RT was administered once daily (one daily fraction of 2 Gy on 5 consecutive days a week), concurrently with chemotherapy. Patients with complete remission (CR) or good partial response (PR) after initial therapy received prophylactic cranial irradiation (PCI). The detailed characteristics of the patients are given in Table 1. All reviews were performed following institutional guidelines and the Declaration of Helsinki 1975 in its most recent version. Ethical approval for the study and a waiver of written informed consent were obtained from the local ethics committee, University

Hospital Heidelberg (#S-461/2016). Patient confidentiality was maintained by anonymizing patient data to remove any identifying information.

Statistical analyses

A statistical analysis was carried out using SigmaPlot™ (Systat Software GmbH, Erkrath, Germany). Univariate Cox proportional HRs were used to assess the influence of cofactors on overall survival (OS). For comparison of survival curves, log-rank (Mantel–Cox) test was used. OS was defined as the time from the first fraction of radiotherapy to death. Living patients were censored from survival analysis at last known contact. A *P* value of <0.05 was considered as statistically significant. NLR was calculated by dividing the number of neutrophils by lymphocyte number. NLR cutoff values of >4 and >2.65 were used to compare the results with previous findings.[11,20]

Results

Univariate analysis for OS revealed a statistically significant effect for LDH >400 (HR 2.05; 95% CI 1.29–3.26; *P*=0.002), PCI (HR 0.58; 95% CI 0.40–0.85; *P*=0.005), CRP >50 (HR 1.49; 95% CI 1.05–2.10; *P*=0.026), and Karnofsky performance scale (KPS) <70% (HR 1.35; 95% CI 1.02–1.80; *P*=0.035). NLR, age (>70 years), Hb, and Pc did not influence survival (Table 2).

In multivariate analysis, OS was significantly affected by PCI (HR 0.64; 95% CI 0.43–0.94; *P*=0.026), LDH >400 (HR 1.91; 95% CI 1.21–3.05; *P*=0.006), and CRP >50 (HR 1.43; 95% CI 1.01–2.04; *P*=0.045). KPS (≤70%) did not influence survival in multivariate analysis (Table 3).

The median OS calculated from the first day of RT was 20 months. Patients who received PCI had a significantly longer survival compared to patients who did not receive PCI

Table 1 Characteristics of the patients

Variable	N=350
Median age (range), years	64 (37–93)
Median KPS % (range)	80 (50–100)
Male, n (%)	213 (61)
Female, n (%)	137 (39)
PCI, n (%)	299 (85)
Median LDH (range), U/L	248 (123–1,136)
Median CRP (range), mg/L	28 (<1–280)
Median Pc (range), /nL	301 (4–909)
Median Hb (range), g/dL	13.8 (8–18)
Median NLR (range)	4 (0.5–18.5)

Abbreviations: KPS, Karnofsky performance scale; PCI, prophylactic cranial irradiation; LDH, lactate dehydrogenase; CRP, C-reactive protein; Pc, platelet count; Hb, hemoglobin; NLR, neutrophil-to-lymphocyte ratio.

Table 2 Univariate proportional hazards regression analysis of cofactors associated with OS

Factors analyzed		HR	95% CI	P
NLR	<2.65	0.86	0.64–1.15	0.32
NLR	<4	0.92	0.71–1.19	0.52
LDH	>400 U/L	**2.05**	1.29–3.26	**0.002**
Hb	g/dL	0.97	0.89–1.05	0.49
Pc	<125/nL	0.5	0.16–1.63	0.25
CRP	>50 mg/L	**1.49**	1.05–2.10	**0.026**
Age, years	>70	1.23	0.93–1.63	0.15
PCI		**0.58**	0.40–0.85	**0.005**
KPS	≤70%	**1.35**	1.02–1.80	**0.035**

Note: Bold values indicate significant cofactors in univariate analysis.
Abbreviations: OS, overall survival; NLR, neutrophil-to-lymphocyte ratio; LDH, lactate dehydrogenase; Hb, hemoglobin; Pc, platelet count; CRP, C-reactive protein; PCI, prophylactic cranial irradiation; KPS, Karnofsky performance scale.

(median 20 vs 12 months; *P*=0.005). Patients with a KPS <70 had a significantly shorter survival compared to patients with a KPS >70 (17 vs 20 months; *P*=0.010; Figure 1). Compared to patients with a CRP <50, patients with a CRP >50 had a significantly longer survival (median 20 vs 14 months; *P*=0.025; Figure 2). Furthermore, an LDH >400 was associated with a significantly shorter survival compared to an LDH <400 (median 13 vs 20 months; *P*=0.008; Figure 3).

Discussion

In the present study, we investigated the relationship between inflammatory markers, such as CRP, NLR, LDH, Hb, and Pc in patients with LD SCLC undergoing TCR. In univariate analysis, serum CRP level and LDH level were significantly

associated with OS. Among the inflammatory markers examined in this study, multivariate analysis revealed that only elevated serum CRP and LDH were predictors of survival. The relevance of pretreatment NLR and Pc noted in previous studies was not confirmed in univariate and multivariate analyses.

In the present study, NLR measured as a continuous variable (results not shown) as well as NLR >4 and>2.65 did not show a significant association with survival and contrasts previous results.[11,20] The underlying mechanisms regarding the prognostic value of NLR are not fully understood but might reflect an increase in inflammation or a decrease in antitumor immunity.[21] Neutrophils have been shown to be inductors of acute-phase proteins, including CRP, which has also been reported to predict poor prognosis in several tumor types.[17,22–26] The present study revealed that elevated CRP is a strong predictor of outcome in LD patients undergoing TCR and confirmed previous studies, showing a significant correlations between elevated serum LDH levels and poor OS in patients with SCLC.

Inflammation plays an important role in tumor progression, and baseline immune suppression and systemic inflammation are associated with inferior survival.[3,4] Inflammation

Table 3 Multivariate proportional hazards regression analysis of cofactors associated with OS

Factors analyzed		HR	95% CI	*P*
LDH	>400 U/L	**1.92**	**1.20–3.05**	**0.006**
CRP	>50 mg/L	**1.43**	1.00–2.04	**0.045**
KPS	≤70%	1.22	0.91–1.64	0.184
PCI	Performed	**0.65**	0.44–0.95	**0.026**

Note: Bold values indicate significant cofactors in multivariate analysis.
Abbreviations: OS, overall survival; LDH, lactate dehydrogenase; CRP, C-reactive protein; KPS, Karnofsky performance scale; PCI, prophylactic cranial irradiation.
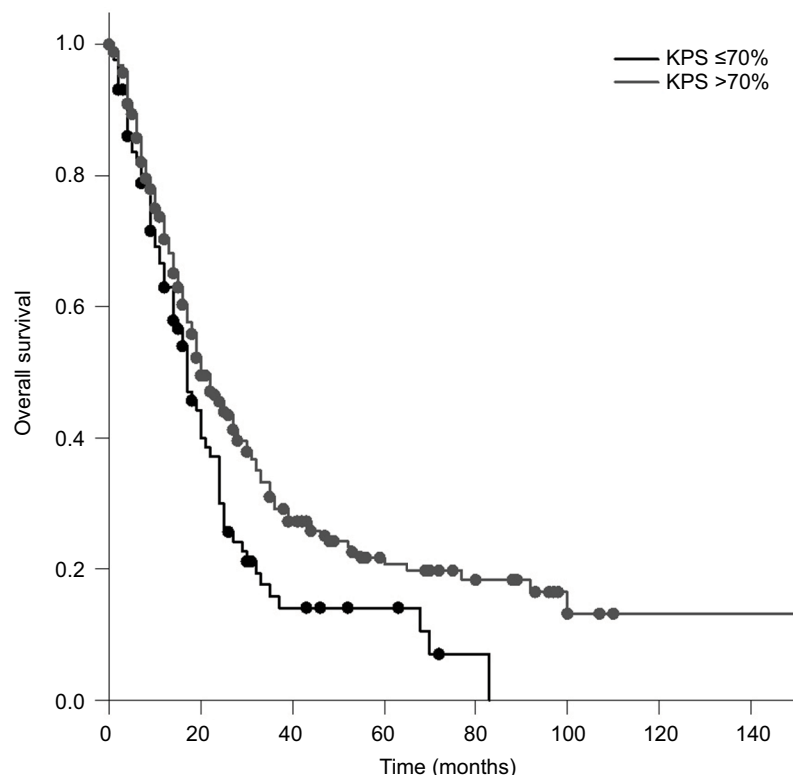

Figure 1 OS in patients with a KPS ≤70% compared to that in patients with a KPS >70% (Kaplan–Meier's estimation, time in months: 17 vs 20 months; *P*=0.010).
Abbreviations: KPS, Karnofsky performance scale; OS, overall survival.
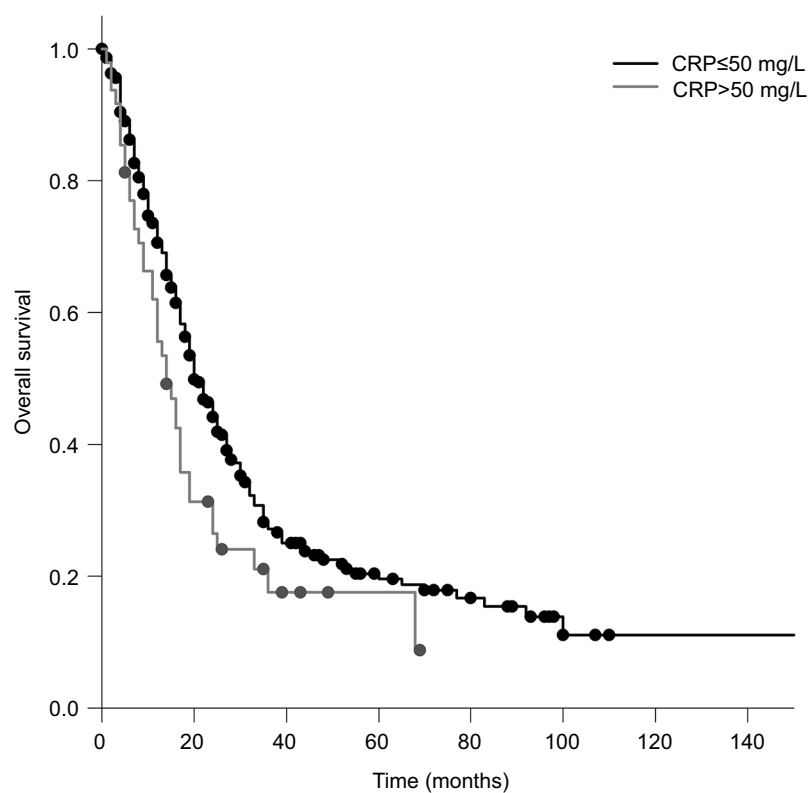
Figure 2 OS in patients with a CRP ≤50 mg/L compared to that in patients with a CRP >50 mg/L (Kaplan–Meier's estimation, time in months: median 20 vs 14 months; *P*=0.025).
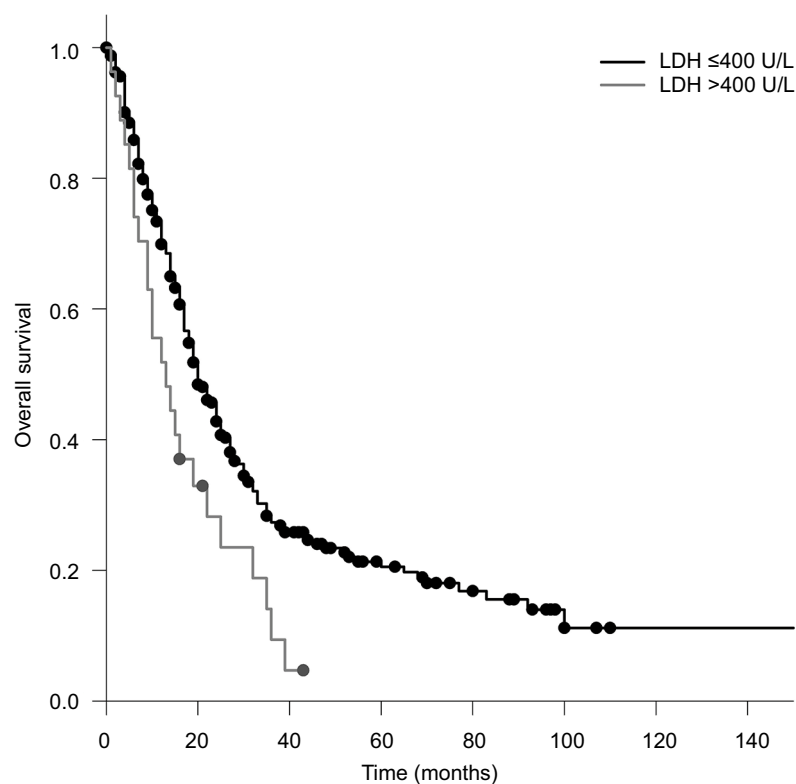**Abbreviations:** CRP, C-reactive protein; OS, overall survival.

Figure 3 OS in patients with an LDH >400 U/L compared to that in patients with an LDH ≤400 U/L (Kaplan–Meier's estimation, time in months: median 13 vs 20 months; *P*=0.008).
Abbreviations: LDH, lactate dehydrogenase; OS, overall survival.

factors, such as CRP, NLR, LDH, and Pc, have been studied in various types of solid tumors and have independent prognostic values across tumor types in patients with advanced cancer.[7,13,24,27–31] Furthermore, NLR is an inexpensive, easy accessible biomarker that has the potential to be helpful with clinical decision making and stratify patients in clinical trials. Several studies also showed the potential benefit of inflammatory markers as prognostic factors in lung cancer patients. A recent meta-analysis revealed that a high NLR had an unfavorable effect on NSCLC patients. A subgroup analysis showed that, compared with other subgroups, the subgroup with a cutoff of 5 had a significantly poorer survival in NSCLC patients.[7] Furthermore, another meta-analysis demonstrated that elevated pretreatment NLR was associated with poor prognosis among patients with lung cancer.[32] Potentially prognostic markers can also serve as indexes for the immune status of the patients and the extent of progression,[17,18] and furthermore, these markers were shown to be predictive of the therapeutic efficacy of immunotherapy.[8,17] In a previous study, NSCLC patients were treated with nivolumab, and an NLR ≥5 prior to therapy was associated with shorter OS. Additionally, patients with lower serum CRP levels had a significantly longer median time to treatment failure.[17] In a prospective observational study, NLR was found to be a potential candidate for a convenient biomarker regardless of PD-L1 expression.[12]

A previous study showed that NLR can be an independent predictor of OS in LD SCLC as an NLR of ≥4 resulted in significantly shorter survival than an NLR of <4.[20] Similar results were published by a Korean group, who also showed that an NLR of >4 and elevated LDH were associated with poor prognosis. Platelet–lymphocyte ratio (PLR) at diagnosis was not associated with OS.[33] However, the number of patients was relatively low, or LD and extensive disease (ED) patients were grouped together (n=64 and n=187, respectively). A Chinese study showed that high NLR >4.55 and PLR >148 were associated with poor overall prognosis and high NLR value, ED stage, and hepatic metastasis were independent prognostic factors in LD and ED SCLC.[34] A large and well-selected retrospective study conducted at the MD Anderson Center investigated the effect of NLR in ED patients (n=252) and found that pretreatment NLR was a useful predictor of outcome in patients treated for ED SCLC. Comparable to the present study, pretreatment Pc was not linked with OS.[35] Another study revealed not only an association between NLR and LDH and survival but also a link between NLR and platinum-sensitivity status.[36] Deng et al[11] observed in a mixed cohort of ED and LD patients that elevated NLR >2.65 before treatment was an independent prognostic factor of poor progression-free survival (PFS) and OS and LDH as an prognostic factor for OS and PFS.

In contrast to our study, several trials were able to show a prognostic value of NLR in lung cancer patients. Currently, there are no defined cutoff values, and several reports have used different cutoff values when evaluating the prognostic value of NLR.[6] We tried to address this issue by using different and previously used cutoff values. Nevertheless, NLR was not found to be prognostic for OS in this cohort. Inflammatory comorbidities, infections, and steroid treatments could be confounding factors. In addition, the timing of blood count might be relevant, as we assessed NLR within 2 weeks prior to the start of chemotherapy because NLR might have been a useful tool for pretherapy stratification of patients. Perhaps, NLR might be useful in prospective oncology monitoring with several time points, but using an NLR cutoff value for clinical decision making prior to any therapy requires extreme caution in SCLC patients. Comparable to NSCLC patients, NLR might be a prognostic marker for SCLC patients undergoing second-line immunotherapy, though currently there are no data available.[37]

This study was limited by its retrospective nature, but we tried to address these biases by presenting a large, well-selected, and homogeneous group of patients.

Conclusion

Our findings suggest that pretreatment-elevated CRP and LDH are prognostic factors for patients with LD SCLC undergoing TCR. LDH and CRP are easy to use and cost-effective. In contrast to previous reports, NLR was not associated with survival measured before the start of TCR. Therefore, the use of NLR as a prognostic tool for treatment stratification prior to therapy in LD SCLC patients must be viewed with caution. Further research is needed to investigate the role of inflammatory markers in SCLC patients undergoing immunotherapy.

Acknowledgments

Disclosure

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