



C-reactive protein and lactate dehydrogenase serum levels potentially predict the response to checkpoint inhibitors in patients with advanced non-small cell lung cancer

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Background: Programmed cell death-ligand 1 (PD-L1) expression and other biomarkers are not completely reliable predictors of the response to checkpoint inhibitors in patients with advanced non-small cell lung cancer (NSCLC). We investigated the value of peripheral serological inflammatory indicators and their combination in predicting the prognosis of patients with advanced NSCLC treated with checkpoint inhibitors.

Methods: This study retrospectively analyzed 116 NSCLC patients treated with anti-programmed cell death protein 1 (PD-1)/PD-L1 monoclonal antibodies. Clinical data of the patients were collected before treatment. X-tile plots determined the optimal cut-point for C-reactive protein (CRP) and lactate dehydrogenase (LDH). A survival analysis was performed using the Kaplan-Meier method. Multi-factor Cox regression analysis was used to evaluate the statistically significant factors identified in the univariate analysis.

Results: The X-tile plots show the cut-points of CRP and LDH were 8 mg/L and 312 U/L, respectively. Univariate analyses showed high baseline serum LDH and low CRP levels were associated with adverse progression-free survival (PFS). Multivariate analyses indicated that CRP (HR, 0.214, 95% CI: 0.053–0.857, P=0.029) could be a predictive indicator for PFS. In addition, we evaluated the combination of CRP and LDH, and univariate analyses showed that patients with high CRP and low LDH exhibited significantly

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better PFS than those in the other groups.

Conclusions: Baseline levels of serum CRP and LDH have the potential to become a convenient clinical tool to predict response to immunotherapy in advanced non-small cell lung cancer.

Keywords: Non-small cell lung cancer (NSCLC); checkpoint inhibitors; C-reactive protein (CRP); lactic dehydrogenase (LDH)

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Introduction

Lung cancer is a malignant tumor with high global morbidity and mortality. More than 50% of patients with lung cancer are diagnosed when the disease is already at an advanced stage (1). Chemotherapy is the standard treatment in most situations. Currently, the effective rates of platinum combination chemotherapy in patients with non-small cell lung cancer (NSCLC) range from 20% to 50% (2). Studies have pointed out that compared with chemotherapy and immunotherapy, immunocombination chemotherapy can further improve the quality of life and survival of patients with advanced NSCLC (3,4).

Although immunotherapy has some advantages, it does not show the same expected benefits for all patients. It was reported that only about 20–25% of NSCLC patients respond positively to immunotherapy (5). Therefore, further research is needed to identify patients who may benefit from immune checkpoint blockade therapy. Effective predictive biomarkers are necessary to achieve personalized treatment

and guide clinical trial designs. In patients with advanced NSCLC, the evaluation of programmed cell death-ligand 1 (PD-L1) expression is used as an important biomarker for selecting patients suitable for anti-PD-L1 treatment (6). Generally, a high PD-L1 expression is predictive of immunotherapy benefits; however, some low-expression populations have also demonstrated benefits (7). Similarly, other potential biomarkers have failed to successfully predict the efficacy of immunotherapy (8). There are only a small number of cancers where mismatch repair, microsatellite instability, and tumor mutation can be used as biomarkers to predict the efficacy of immunotherapy (9).

Recently, research efforts in immunotherapy for lung cancer have begun to focus on the concentration of plasma inflammatory markers, such as lactate dehydrogenase (LDH) and C-reactive protein (CRP) (10–12). Although most inflammatory molecular markers are non-specific inflammatory markers, some studies suggest that they can participate in the occurrence and development of many kinds of malignant tumors. For example, one study suggested that increased preoperative CRP levels are associated with the inability to achieve complete resection in patients with NSCLC (13), and another study showed that changes in CRP in the early stage can predict response to checkpoint inhibitor treatment (14). It is suggested that systemic inflammatory response plays an important role in the occurrence and development of cancer and is related to the therapeutic effect for tumor patients. It has been reported that inflammatory markers have far-reaching effects on cancer development and the innate immune system (15), but the presumptive prognostic value of combined serum inflammatory molecular markers in NSCLC patients receiving immunotherapy has not yet been fully explored.

In this study, we analyzed the clinical significance of CRP and LDH to establish their association with tumor response

Highlight box

Key findings

- CRP and LDH serum levels and their combination may predict the response to checkpoint inhibitors in patients with NSCLC.

What is known, and what is new?

- CRP and LDH serum levels are reported to correlate with different prognoses in NSCLC patients treated with checkpoint inhibitors.
- We established an association between CRP, LDH, and their combination with tumor response and prognosis in NSCLC patients treated with checkpoint inhibitors.

What is the implication, and what should change now?

- LDH, CRP, and their combination are potential predictive biomarkers of clinical response and need to be incorporated into future clinical trials.

and prognosis in patients with advanced NSCLC treated with checkpoint inhibitors. We present the following article in accordance with the REMARK reporting checklist (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-240/rc>).

Methods

Study design

The medical records of 116 patients with NSCLC were retrospectively reviewed from the 900th Hospital of the Joint Logistic Support Force from January 1, 2019, to March 1, 2022. The demographic data included gender, age, and smoking history. The clinical data included pathological type, gene mutation, granulocyte count, baseline CRP, baseline LDH, expression of tumor PD-L1, and objective response. Progression-free survival (PFS) was the primary endpoint and was assessed by investigators according to the Response Evaluation Criteria in Solid Tumors modified for immune-based therapeutics (iRECIST) (16). All baseline hematological parameters were obtained retrospectively 3 weeks before treatment as a result of normal medical practice.

Patients

Patients were included in the study if they had inoperable stage III–IV NSCLC confirmed by histopathology and were eligible to receive anti-PD-1/PD-L1 immunotherapy (single or combination regimen). All patients use at least one of the following immune checkpoint inhibitors (ICIs): Pembrolizumab, Tislelizumab, Sintilimab, Camrelizumab, Nivolumab, Toripalimab, Atezolizumab. The combination regimen is platinum-containing dual-drug chemotherapy, determined according to tumor histology. The treatment and outcome of each line were obtained. The Eastern Oncology Collaboration Group (ECOG) physical status score was 0–2 before taking treatment. Patients were excluded if they could not tolerate checkpoint inhibitors, had other primary malignant tumors, had received antibiotic therapy within the previous 3 weeks, or had been diagnosed previously with hematological or immune system diseases. The tumor stage was defined in accordance with the American Joint Committee on Cancer/International Union Against Cancer tumor-node-metastasis (TNM) classification system. Efficacy data were evaluated according to iRECIST. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study

was approved by the institutional ethics board of the 900th Hospital of the Joint Logistic Support Force, PLA (No. 2022-028). Individual consent for this retrospective analysis was waived.

Statistical analysis

X-tile software version 3.6.1 (Yale University School of Medicine, New Haven, CT, USA) was used to determine the optimal cutoff values of CRP and LDH. Patients were then divided into high and low groups. PFS was estimated using the Kaplan-Meier method, and the resultant curves were statistically tested by the log-rank method. Hazard ratios were estimated with the use of a stratified Cox regression model. All statistical test results were considered statistically significant at $P < 0.05$. All statistical analyses were performed using SPSS Software version 25.0 (IBM Corporation, Armonk, NY, USA).

Results

Patient characteristics

Characteristics of the 116 patients with stage III–IV NSCLC who received checkpoint inhibitors between January 2019 and June 2022 are shown in *Table 1*. They included 88 (75.9%) men and 28 (24.1%) women. The median age of patients was 59.5 years (range, 26–78 years), and the median follow-up time was 5 months (range, 1–35 months). Of the 116 patients, 83 showed disease progression or died during follow-up. Overall, 35% of patients were current or former smokers.

The optimum cut-point for CRP and LDH

The X-tile program was used to determine the cut-points for CRP and LDH and to assess statistical significance. According to the X-tile plots, the cut-points were as follows: CRP (8 mg/L) and LDH (312 U/L). These optimal cut-points most appropriately divided the cohort (*Figure 1*). We defined patients with CRP < 8 mg/L as the low CRP group, CRP ≥ 8 mg/L as the high CRP group, LDH < 312 U/L as the low LDH group, and LDH ≥ 312 U/L as the high LDH group.

Efficacy of checkpoint inhibitors according to baseline CRP and LDH

We evaluated whether baseline CRP and LDH showed

Table 1 Patient characteristics

Characteristic	Values
Age (years), median [range]	59.5 [26–78]
Age (years), n (%)	
<60	66 (56.9)
≥60	50 (43.1)
Gender, n (%)	
Male	88 (75.9)
Female	28 (24.1)
Smoking status, n (%)	
Never	76 (65.5)
Current or former	40 (34.5)
PD-L1 status, n (%)	
0	11 (9.5)
0–50%	8 (5.9)
>50%	14 (12.1)
Histology, n (%)	
Squamous	37 (31.9)
Non-squamous	79 (68.1)
TNM stage, n (%)	
IIIB–IIIC	9 (7.8)
IVA–IVB	107 (92.2)

PD-L1, programmed cell death-ligand 1; TNM, tumor-node-metastasis.

effects in PFS. A Kaplan-Meier analysis was used to evaluate every marker on patients' survival. The results demonstrated high LDH and low CRP levels were associated with adverse PFS (Figure 2).

The predictive value of joint indicators: the combination of CRP and LDH

To further explore the value of CRP and LDH levels, patients were classified into four groups based on CRP (\geq and <8 mg/L) and LDH (\geq and <312 U/L) (Figure 2). A: CRP_{High} with LDH_{Low} (n=36); B: CRP_{High} with LDH_{High} (n=6); C: CRP_{Low} with LDH_{Low} (n=38); D: CRP_{Low} with LDH_{High} (n=2) (Table 2). The Kaplan-Meier survival analysis indicated statistical significance ($P=0.002$), as shown in Figure 3A. Patients with CRP_{High} and LDH_{Low} exhibited significantly better PFS than others. Therefore, we subsequently merged the four groups into two (CRP_{High} with LDH_{Low} versus others). The CRP_{High} and LDH_{Low} group had a significantly better objective response rate (ORR) and PFS than other combinations (ORR: 51.2% vs. 21.2%, and PFS: 10.0 vs. 5.3 months, $P=0.007$) (Figures 3,4).

Association between PFS and inflammatory molecular markers: univariate and multivariate Cox regression analysis

According to the results of univariate analysis, CRP (HR, 0.538; 95% CI: 0.334–0.866, $P=0.011$) and PD-L1 status

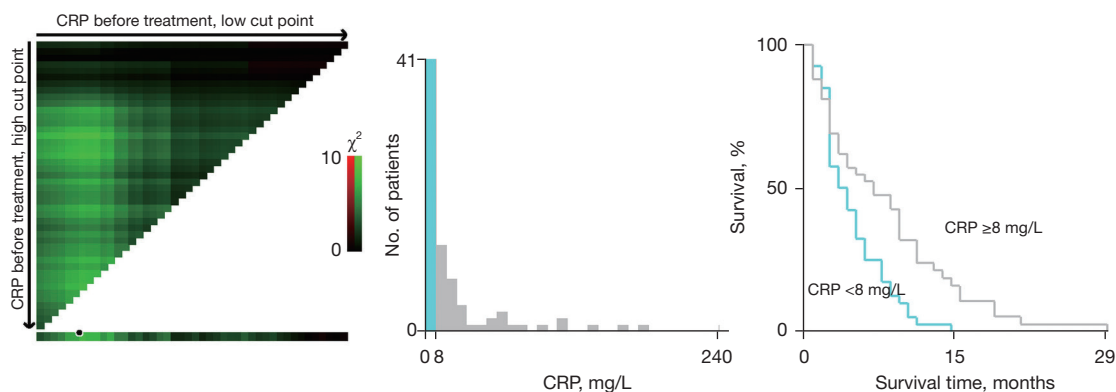


Figure 1 X-tile plots determine the cutoff value for CRP before using checkpoint inhibitors. The χ^2 log-rank values created when the cohort was divided into two groups are shown in the left image. The cut-point is highlighted by the black circle in the left image and demonstrated by a histogram of the cohort (middle image) and a Kaplan-Meier plot (right image). Cutoffs for LDH were obtained by the same method. CRP, C-reactive protein; LDH, lactate dehydrogenase.

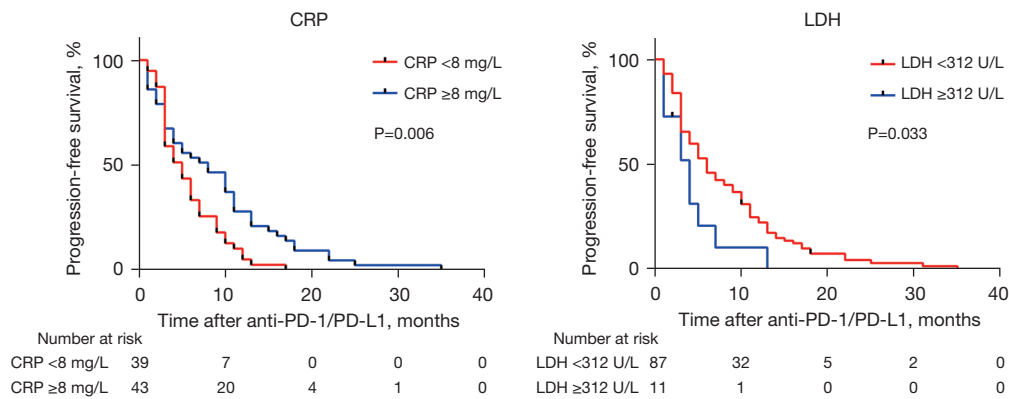


Figure 2 Kaplan-Meier survival analysis of CRP and LDH in patients (log-rank test). CRP: <8 mg/L, n=39; ≥8 mg/L, n=43. LDH: <312 U/L, n=87; ≥312 U/L, n=11. CRP, C-reactive protein; LDH, lactic dehydrogenase; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

Table 2 Different combinations of CRP and LDH

Combinations	CRP _{High}	CRP _{Low}	Total
LDH _{High}	6	2	8
LDH _{Low}	36	38	74
Total	42	40	82

CRP, C-reactive protein; LDH, lactic dehydrogenase.

(HR, 0.312; 95% CI: 0.130–0.747, P=0.009) showed a statistical significance (Table 3). Because some of the variables in the univariate analysis were covariates, we performed a multivariate analysis of gender, age, pathology, stage, smoking status, CRP, LDH, and PD-L1 status. In our cohort, only CRP was identified as a significant independent prognostic factor for PFS.

Discussion

For patients with advanced NSCLC, immunotherapy is approved as a first-line treatment. However, checkpoint inhibitors can cause serious adverse reactions (17,18), so it is particularly important to predict their efficacy. Although pathological subtypes, PD-L1 expression levels, tumor mutational burden (TMB) status, and microsatellite instability can predict checkpoint inhibitor efficacy (19), the detection methods of these biomarkers are complex and expensive (20). Therefore, it is particularly important to predict the effectiveness of checkpoint inhibitors using routine laboratory test indicators.

Inflammation is known to play an important role in

tumor occurrence and development (21) and impacts the prognosis of NSCLC and tumor checkpoint inhibitors (22). Studies have shown that tumors can grow and evade immune surveillance by generating inflammatory and anti-inflammatory signals (23). Among them, inflammation-related markers, such as CRP and LDH, may play a key role in this process (24).

In this study, we found that baseline CRP and LDH levels had prognostic value in the immunotherapy of NSCLC. Further analysis using the optimal cut-off value (CRP: 8 mg/L; LDH: 312 U/L) demonstrated that patients with higher baseline CRP and lower baseline LDH showed better PFS than those with lower CRP and higher LDH levels. PD-L1 positivity alone was not an independent prognostic factor; possibly because blocking the PD-1 pathway did not affect the inflammatory microenvironment and lead to a T-cell response to cancer cells.

CRP is a classic and widely used serum indicator for evaluating the acute-phase response in the internal environment (25). Several studies have reported the significance of CRP as an important factor in predicting prognosis in NSCLC (26,27). LDH is the main enzyme in glycolysis and a classical indicator of tumor metabolism. It has previously been examined by researchers as a predictor of response to checkpoint inhibitors. Some studies have reported that an elevated serum CRP value was associated with inferior survival in NSCLC patients who received checkpoint inhibitors (28,29). However, the function of CRP in tumor progression and checkpoint inhibitor use remains controversial, and the unique role of various inflammatory factors remains unclear. One study

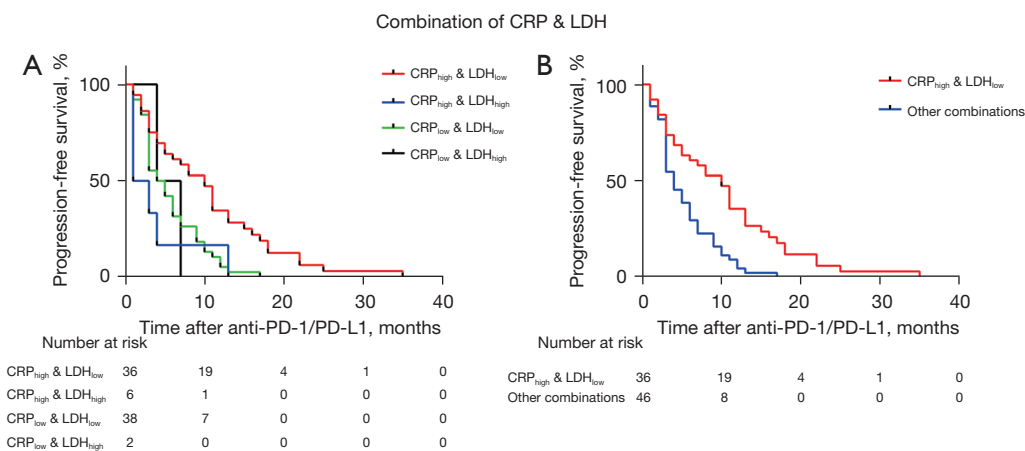
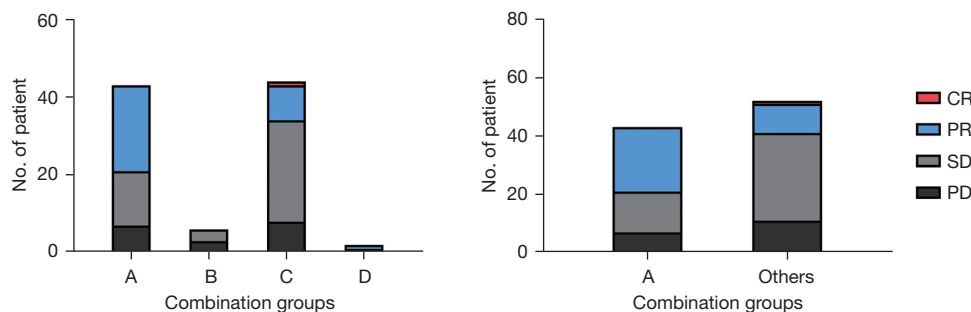


Figure 3 Kaplan-Meier survival analysis according to four different combinations of CRP and LDH (log-rank test). (A) Red line, CRP_{High} with LDH_{Low} (n=36); blue line, CRP_{High} with LDH_{High} (n=6); green line, CRP_{Low} with LDH_{Low} (n=38); black line, CRP_{Low} with LDH_{High} (n=2) (P=0.002). (B) Red line, CRP_{High} with LDH_{Low} (n=36); blue line, other combinations (n=46). CRP, C-reactive protein; LDH, lactic dehydrogenase. PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.



reported that in the early stage of checkpoint inhibitor use, some patients with elevated CRP demonstrated a better prognosis (14), and other research has indicated that some inflammatory cytokines promote an anti-tumor response in the body (30). A recent study reported that the immune-inflamed tumor phenotype is strongly infiltrated with T-cells and is more often responsive to PD-L1 inhibitors (31) and that the cytokines released by T-cells may promote increased CRP levels. Other studies have found that CRP suppresses the response of T-helper cells (32,33) and delays tumor progression (34). Pyroptosis is an inflammatory form of cell death triggered by certain inflammasomes (35). Recent studies have shown that cytokines promoting

the rapid synthesis of CRP, such as IL-1 β and IL-18, are produced during pyroptosis and may enhance the efficacy of checkpoint inhibitors, including ICIs and CAR-T cells (36,37). CRP can also indirectly affect the efficacy of immunotherapy by affecting other prognostic markers, such as increase the PD-L1 expression in NSCLC, and improve the response of NSCLC to checkpoint inhibitors (38). Other reasons for the differences may be the difference in the population included in each study and the difference in the method and value of the optimal cut-off value of serum CRP. Some studies did not exclude patients with infection, and these patients usually combined with elevated CRP, and the prognosis is worse than normal patients.

Table 3 Univariate and multivariate Cox proportional hazards regression analysis of predictive classifications for PFS

Characteristic	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Gender (male vs. female)	1.028	0.644–1.643	0.907	1.130	0.173–7.389	0.899
Age (<60 vs. ≥60 years)	0.874	0.580–1.315	0.518	1.437	0.424–4.870	0.560
Pathology (squamous vs. non-squamous)	0.700	0.442–1.106	0.126	0.402	0.106–1.529	0.181
Stage (IIIB–C vs. IV)	1.298	0.591–2.852	0.516	2.098	0.106–26.447	0.567
Smoking status (never vs. current or former)	0.759	0.485–1.187	0.226	0.826	0.236–2.890	0.765
CRP (<8 vs. ≥8 mg/L)	0.538	0.334–0.866	0.011	0.214	0.053–0.857	0.029
LDH (<312 vs. ≥312 U/L)	1.942	0.995–3.789	0.052	2.822	0.820–9.716	0.100
PD-L1 status (0 vs. >0)	0.312	0.130–0.747	0.009	0.771	0.213–2.788	0.692

CRP, C-reactive protein; PFS, progression-free survival; LDH, lactate dehydrogenase, PD-L1, programmed cell death-Ligand 1; HR, hazard ratio; CI, confidence interval.

To correct the inaccuracy of a single biomarker in predicting prognosis in patients with NSCLC, we combined LDH and CRP as joint indicators to provide a more accurate assessment of prognosis for these patients. To the best of our knowledge, this is the first study to investigate the use of combined CRP and LDH as a prognostic factor for checkpoint inhibitors. Our study demonstrated that patients in Group A (CRP_{High} with LDH_{Low}) had significantly better PFS and ORR than those in groups B, C, and D. This result suggests that the relationship between CRP and LDH in NSCLC immunotherapy needs further exploration. The limitations of this preliminary study were the limited sample size and the fact that the oncological results were retrospectively evaluated. Moreover, CRP is a non-specific parameter and is elevated in many situations, including infections, inflammatory diseases, tissue damage, and many other cancers (39). Furthermore, the molecular markers were all measured before treatment, and it is unclear whether subsequent changes have a role in prognostic assessment. Nevertheless, it cannot be ignored that these biomarkers have the advantage of being affordable and easy to access.

Conclusions

In this study, our data suggest that patients with high CRP levels and low LDH levels show better survival with anti-PD-1/PD-L1 therapy. LDH, CRP, and their combination are potential predictive biomarkers of clinical benefits and need to be incorporated into future clinical trials.

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Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-240/rc>

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-240/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki

(as revised in 2013). The study was approved by the institutional ethics board of the 900th Hospital of the Joint Logistic Support Force, PLA (No. 2022-028). Individual consent for this retrospective analysis was waived.

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