

# Potential predictive value of plasma heat shock protein 90 $\alpha$ in lung cancer

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## Abstract

**Objective:** Heat shock protein 90 $\alpha$  (HSP90 $\alpha$ ) is associated with cancer development, progression, and metastasis. This study assessed the relationships of plasma HSP90 $\alpha$  levels with treatment efficacy and prognosis in lung cancer.

**Methods:** In this retrospective cross-sectional study, 231 patients with lung cancer were enrolled from 1 September 2016 to 31 December 2019. HSP90 $\alpha$  levels were measured before and after treatment, and their relationships with outcomes were assessed.

**Results:** Patients with elevated HSP90 $\alpha$  levels before treatment had a better overall response rate (ORR, 44.1% vs. 30.6%), whereas the disease control rate did not differ between patients with elevated and normal HSP90 $\alpha$  levels (81% vs. 78.5%). Median progression-free survival (PFS) was 6.9 months in patients with elevated baseline HSP90 $\alpha$  levels, versus 9 months in patients with normal HSP90 $\alpha$  levels, whereas the median overall survival (OS) times in these groups were 12 and 14.1 months, respectively. Concerning HSP90 $\alpha$  levels after treatment, ORR (20% vs. 47.1%) and DCR (67.3% vs. 90.9%) were lower in patients with increased HSP90 $\alpha$  levels, and PFS and OS were also significantly different between the groups.

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**Conclusions:** HSP90 $\alpha$  levels before and after treatment were associated with treatment response and patient prognosis in lung cancer.

### Keywords

Heat shock protein 90 $\alpha$ , treatment response, progression-free survival, overall survival, lung cancer, prognosis, biomarker

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## Introduction

Lung cancer is the most common cancer worldwide and the leading cause of malignant tumor death.<sup>1,2</sup> The incidence of lung cancer in China has significantly increased, making this disease a common health hazard.<sup>3,4</sup> Because many patients are diagnosed after disease progression, early detection and diagnosis are the most important measures for preventing lung cancer death.<sup>5</sup> There has been substantial progress in the treatment of lung cancer recently, such as the development of targeted therapy and immunotherapy, but the identification of biomarkers has been slow.<sup>6,7</sup> In fact, there is no good biomarker to predict and monitor therapeutic efficacy in lung cancer at present. In the clinic, many techniques are used to diagnose and monitor lung cancer, such as the use of specific tumor markers, X-ray, computed tomography, and positron emission tomography-computed tomography, but they all have certain limitations.<sup>8</sup> Therefore, there is an urgent need to identify new strategies for efficiently monitoring or forecasting treatment efficacy in lung cancer.

Heat shock proteins (HSPs) are named according to their molecular weight. HSP90 has four isoforms, namely HSP90 $\alpha$ , HSP90 $\beta$ , tumor necrosis factor receptor-associated protein 1, and glucose related protein 94.<sup>5</sup> HSPs are associated

with several cancer types, such as breast, gastric, and colorectal cancers.<sup>9–11</sup> At present, it is known that HSP90 $\alpha$  is associated with cancer development, progression, and metastasis, mainly because of the presence of HSP90 $\alpha$  on the cell surface.<sup>12–14</sup> However, to the best of our knowledge, few studies with large sample sizes have reported the relationship of plasma HSP90 $\alpha$  levels with therapeutic efficacy or prognosis in lung cancer.

In this study, we measured HSP90 $\alpha$  levels in patients with locally advanced or metastatic lung cancer before and after treatment to assess the relationships of HSP90 $\alpha$  levels and their variations with treatment response and prognosis. Subgroup analyses were also conducted to further determine whether HSP90 $\alpha$  is a good biomarker for evaluating treatment efficacy and prognosis.

## Materials and Methods

### Patients

Patients treated for lung cancer between 1 September 2016 and 31 December 2019 at Sichuan Cancer Hospital were eligible for enrollment. The inclusion criteria were as follows: newly diagnosed lung cancer confirmed by pathology; locally advanced or metastasis disease; no receipt of radical surgery for primary or metastasis lesions;

presence of measurable lesions according to the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1); completion of least two cycles of treatment and an efficacy evaluation; and available HSP90 $\alpha$  test results before and after treatment. The exclusion criteria were as follows: presence of other malignancies; therapy was delayed for more than 28 days; and baseline or post-treatment HSP90 $\alpha$  data were unavailable. This study was approved by the Institutional Review Board of Sichuan Cancer Hospital (approval number: SCCHEC-01A-2021-011). As a retrospective study, the requirement for informed consent was waived, and all patient details have been de-identified.

### Methods

Baseline patient characteristics, treatment responses, and plasma HSP90 $\alpha$  protein levels were recorded before and after two cycles of treatment. Plasma HSP90 $\alpha$  levels were detected using an ELISA kit (Yantai Protgen Biotechnology Development Co., Ltd, Yantai, China). Treatment responses were evaluated using radiological images and the electronic medical record. According to RECIST 1.1, treatment responses were evaluated as complete response (CR), partial response (PR), stable disease (SD), or progression disease (PD). The disease control rate (DCR) was calculated as follows:  $DCR = (CR + PR + SD)/n$  ( $n$  is the total number of patients). The overall response rate (ORR) was calculated as follows:  $ORR = (CR + PR)/n$ . Progression-free survival (PFS) was defined as the period from date of histological diagnosis to that of confirmed progression disease. Overall survival (OS) was defined as the time from diagnosis to death from any cause with censoring at the time of last follow-up. The reporting of this study conforms to the STROBE guidelines.<sup>15</sup>

### Statistical analysis

The cutoff baseline HSP90 $\alpha$  level was obtained using receiver operator characteristic curve analysis. ORR and DCR were compared between the groups using the  $\chi^2$  test (Fisher's exact test if necessary). Survival analysis in the different cohorts was performed using Kaplan–Meier curves and the log-rank test. All statistical analyses were performed using GraphPad Prism 7 (GraphPad Software, Inc., La Jolla, CA, USA), and  $P < 0.05$  indicated statistical significance.

## Results

### Patient characteristics

Data for more than 900 consecutive patients lung cancer treated between 1 September 2016 and 31 December 2018 at Sichuan Cancer Hospital were reviewed, but most patients were excluded because they underwent surgical excision, lacked evaluable lesions, or failed to undergo HSP90 $\alpha$  measurements before or after treatment. Finally, 231 patients with lung cancer were included in the analysis. The cohort included 158 (68.4%) men and 73 (31.6%) women. In total, 175 (75.7%) patients were younger than 65 years old, whereas 56 patients were at least 65 years old (24.3%). Regarding the lung cancer type, non-small cell lung cancer (NSCLC) was present in 160 (69.3%) patients, whereas 71 (30.7%) patients were diagnosed with small cell lung cancer (SCLC). Most patients (191, 82.7%) had stage IV NSCLC or extensive SCLC, whereas only 40 (17.3%) patients had stage III NSCLC or limited SCLC. More patient details are presented in Table 1.

### HSP90 $\alpha$ is associated with treatment response in lung cancer

Among patients with elevated baseline HSP90 $\alpha$  levels ( $\geq 82.06$  ng/mL), 49 patients

**Table 1.** Baseline characteristics of patients with lung cancer.

Group	Number (%)	Median baseline HSP90 $\alpha$ , ng/mL (range)
Entire cohort	231 (100)	78.2 (20.1–606.9)
Sex		
Male	158 (68.4)	78.6 (20.1–606.9)
Female	73 (31.6)	76.6 (31.1–261.7)
Age (years)		
<65	175 (75.7)	82.2 (20.1–606.9)
$\geq$ 65	56 (24.3)	73.1 (26.4–233.7)
Histologic type		
Squamous cell carcinoma	47 (20.3)	78.4 (26.4–512.5)
Adenocarcinoma	105 (45.5)	74.3 (20.1–253.0)
SCLC	71 (30.7)	83.5 (27.5–606.9)
Others	8 (3.5)	111.3 (34–268.6)
Tumor stage		
III (NSCLC)	23 (10.0)	97.2 (35.6–512.5)
IV (NSCLC)	138 (59.7)	74.7 (20.1–467.5)
Limited (SCLC)	17 (7.3)	63.4 (27.5–174.4)
Extensive (SCLC)	53 (23.0)	92.6 (31.1–606.9)

NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; HSP90 $\alpha$ , heat shock protein 90 $\alpha$ .

**Table 2.** Associations of baseline and post-treatment HSP90 $\alpha$  levels with the treatment response.

	Baseline (%)		<i>P</i>	Post-treatment (%)		
	$\geq$ 82.06 ng/mL	<82.06 ng/mL		Increased	Decreased	<i>P</i>
ORR	44.1	30.6	0.033*	20.0	47.1	<0.001*
DOR	81.0	78.5	0.651	67.3	90.9	<0.001*

\*Significant at  $P < 0.05$ .

HSP90 $\alpha$ , heat shock protein 90 $\alpha$ ; ORR, objective response rate; DCR, disease control rate.

achieved CR or PR, and 40 patients were deemed to have SD. Meanwhile, among patients with normal baseline HSP90 $\alpha$  levels (<82.06 ng/mL), 37 patients achieved CR or PR, and 58 had SD. ORR significantly differed between the elevated and normal HSP90 $\alpha$  level groups (44.1% vs. 30.6%,  $P < 0.05$ ). Among patients with increased HSP90 $\alpha$  levels after treatment, 22 achieved CR or PR, and 52 had SD. Among patients with decreased HSP90 $\alpha$  levels after treatment, 57 achieved CR or PR, and 53 patients had SD. ORR (20% and 47.1%,  $P < 0.001$ ) and DCR

(67.3% vs. 90.9%,  $P < 0.001$ ) were both significantly lower among patients with increased HSP90 $\alpha$  levels after treatment (Table 2).

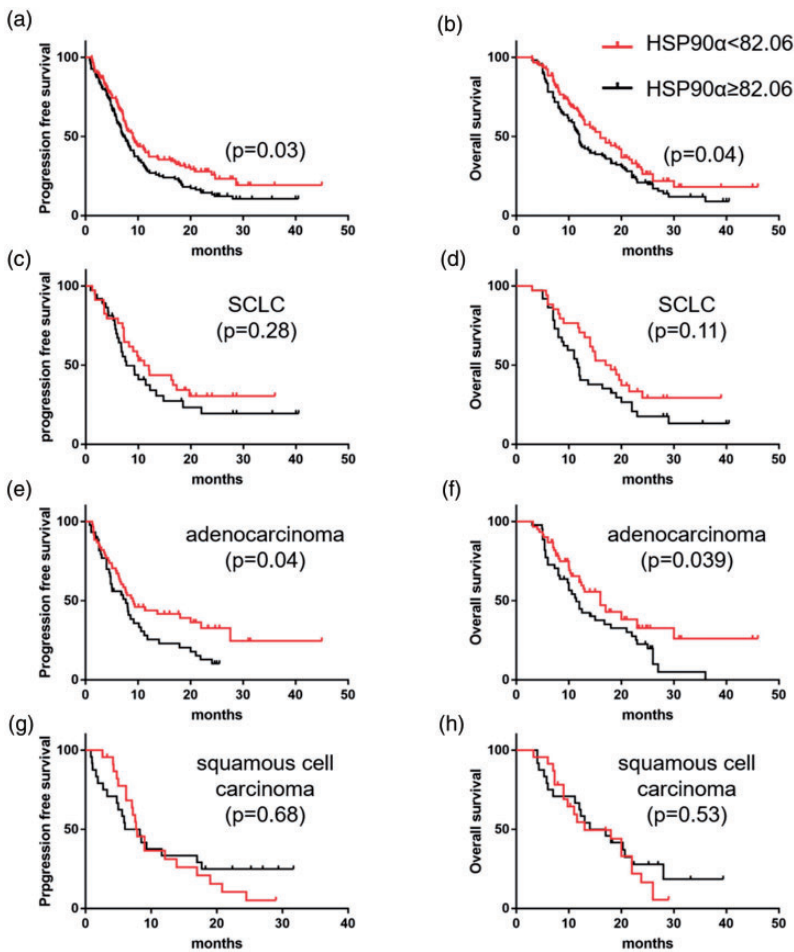
### *PFS and OS according to the HSP90 $\alpha$ level*

Median PFS was 6.9 months in patients with elevated baseline HSP90 $\alpha$  levels, versus 9 months among those with normal baseline HSP90 $\alpha$  levels ( $P < 0.05$ ), whereas the median OS times among patients with elevated and normal baseline HSP90 $\alpha$  levels

were 12 and 14.1 months, respectively ( $P < 0.05$ , Figure 1a–b). Further subgroup analysis was also conducted. Among patients with SCLC, elevated baseline HSP90 $\alpha$  levels indicated a worse prognosis, albeit without significance (Figure 1c–d). For patients with adenocarcinoma, normal baseline HSP90 $\alpha$  levels represented a good prognostic factor ( $P < 0.05$ , Figure 1e–f). For squamous cell carcinoma patients,

there was no significant difference in survival between the two groups (Figure 1g–h).

Outcomes also differed between patients with increased and decreased HSP90 $\alpha$  levels after treatment. Median PFS was 6.9 months among patients with increased levels, versus 9.1 months among those with decreased levels (Figure 2a–b). Among patients with SCLC, elevated HSP90 $\alpha$  levels indicated a worse prognosis, albeit



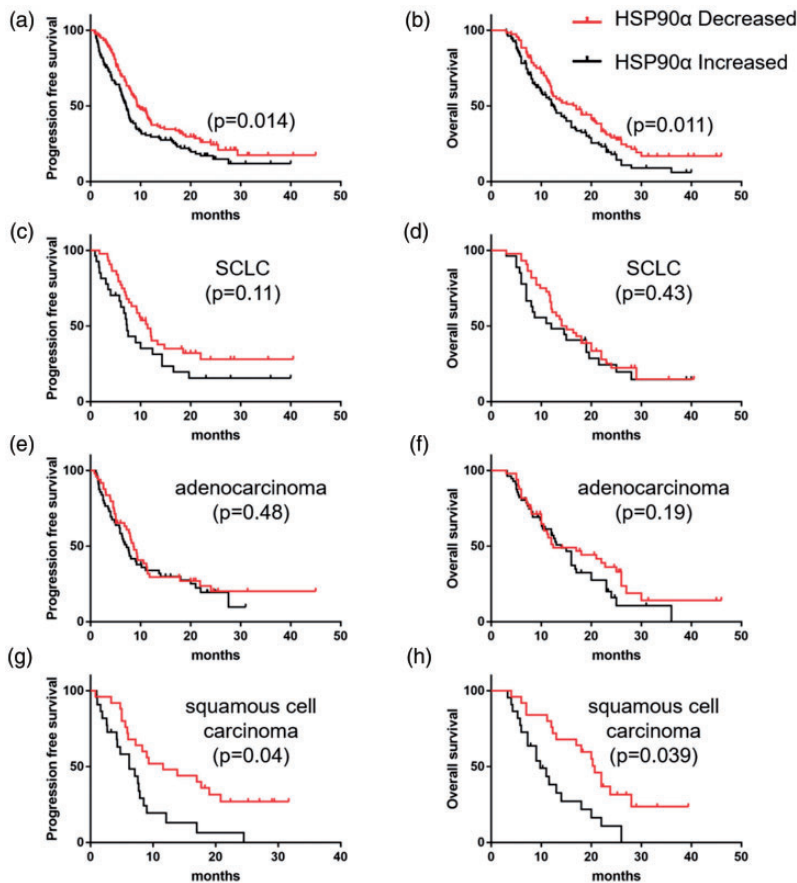
**Figure 1.** PFS and OS according to baseline HSP90 $\alpha$  levels in patients with lung cancer. (a) PFS in the entire study cohort. (b) OS in the entire study cohort. (c) PFS among patients with SCLC. (d) OS among patients with SCLC. (e) PFS among patients with adenocarcinoma. (f) OS among patients with adenocarcinoma. (g) PFS among patients with squamous cell carcinoma. (h) OS among patients with squamous cell carcinoma. PFS, progression-free survival; OS, overall survival; HSP90 $\alpha$ , heat shock protein 90 $\alpha$ ; SCLC, small cell lung cancer.

without significance (Figure 2c–d). Among patients with adenocarcinoma, outcomes did not differ according to the HSP90 $\alpha$  level (Figure 2e–f). Regarding patients with squamous cell carcinoma, normal HSP90 $\alpha$  levels portended a good prognosis ( $P < 0.05$ , Figure 2g–h).

## Discussion

Lung cancer accounts for more than 20% of cancer-related deaths globally, making it

the deadliest cancer.<sup>16</sup> A good tumor bio-marker is extremely important for improving diagnosis and survival. In this study, we analyzed the relationships of baseline plasma HSP90 $\alpha$  levels and their changes after treatment with treatment efficacy and prognosis. We found that baseline HSP90 $\alpha$  levels and their changes after treatment were associated with treatment responses and prognosis in patients with locally advanced or metastasis lung cancer. Subgroup analysis illustrated that



**Figure 2.** PFS and OS according to the changes of HSP90 $\alpha$  levels after treatment. (a) PFS in the entire study cohort. (b) OS in the entire study cohort. (c) PFS among patients with SCLC. (d) OS among patients with SCLC. (e) PFS among patients with adenocarcinoma. (f) OS among patients with adenocarcinoma. (g) PFS among patients with squamous cell carcinoma. (h) OS among patients with squamous cell carcinoma. PFS, progression-free survival; OS, overall survival; HSP90 $\alpha$ , heat shock protein 90 $\alpha$ ; SCLC, small cell lung cancer.

the prognosis of patients with adenocarcinoma differed between those with elevated and normal baseline HSP90 $\alpha$  levels. After grouping patients based on the changes of HSP90 $\alpha$  levels after treatment, the results illustrated lower HSP90 $\alpha$  levels after treatment were associated with better therapeutic efficacy and longer survival. Similarly, the prognosis of patients with squamous cell carcinoma also differed according to the change of HSP90 $\alpha$  levels after treatment.

A few studies demonstrated that altered HSP90 $\alpha$  levels can serve as a biomarker for different cancers. Wang and colleagues demonstrated that HSP90 $\alpha$  levels were higher in most patients with lung cancer and associated with cancer development,<sup>17</sup> suggesting the utility of HSP90 $\alpha$  as a potential diagnostic and prognostic marker in clinical practice. Some previous studies illustrated that HSP90 inhibitors had potent antitumor activity, and they could overcome resistance to chemotherapy and radiotherapy, also suggesting that HSP90 $\alpha$  may be a potential biomarker for cancers, including lung cancer.<sup>18–23</sup> Shi and colleagues reported that HSP90 $\alpha$  levels significantly differed between patients with PD and SD. Our study further demonstrated that changes of plasma HSP90 $\alpha$  protein levels could be a useful biomarker for monitoring treatment response and predicting survival in patients with lung cancer.

In a recent study, Zhong's group explored the association of HSP90 $\alpha$  with chemotherapy in advanced NSCLC. They found that plasma HSP90 $\alpha$  levels can be considered a valuable predictor of early chemotherapy effectiveness in patients with advanced NSCLC, and its levels were positively correlated with tumor remission after chemotherapy.<sup>24</sup> This was similar to our findings. Based on previous research, cancer cells are more dependent on HSP90 $\alpha$  than normal cells, and high HSP90 $\alpha$  expression thus encourages the growth and survival of tumors.<sup>25,26</sup>

Rong's group indicated that HSP90 upregulation was associated with poor post-surgical survival time and lymphatic metastasis in patients with lung cancer.<sup>27</sup> Our results demonstrated that patients with elevated baseline HSP90 $\alpha$  levels had shorter PFS and OS. The higher ORR of patients with elevated baseline HSP90 $\alpha$  levels may also indicated that HSP90 $\alpha$  levels are associated with sensitivity to treatment. Nevertheless, further studies are needed to confirm this finding.

In clinical practice, many plasma proteins have been used as biomarkers for cancer diagnosis, such as CEA and CA125. However, few measurable and useful tumor markers are available, especially markers that can predict treatment efficacy and survival benefit. In our study, we found that both baseline and post-treatment HSP90 $\alpha$  levels were associated with ORR, DCR, PFS, and OS. The results are interesting, as they indicated that baseline HSP90 $\alpha$  elevation is a good marker for ORR and that decreased HSP90 $\alpha$  levels after treatment represented a good biomarker for lung cancer. As a retrospective study, this study had several limitations. First, it was a single-center study. Second, the sample size was not large. Thus, more prospective clinical trials are needed to confirm these results.

## Conclusions

This study may be the first to reveal the role of dynamic changes of HSP90 $\alpha$  for monitoring the response to systemic treatment and predicting survival in patients with lung cancer. The study demonstrated that baseline HSP90 $\alpha$  levels and their changes after treatment are both associated with treatment response and prognosis.

## Availability of data and materials

All analyzed data are included in this published article. The original data are available from the corresponding author upon reasonable request.

### Authors' contributions

XQL and JG conceived the study and performed the statistics analyses. BL and JL performed the data collection. XQL and XST wrote the manuscript. BL and JG critically revised the article for essential intellectual content and provided administrative support. All authors read and approved the final manuscript.


### Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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