

Research Paper

# Serum expression level of IL-6 at the diagnosis time contributes to the long-term prognosis of SCLC patients

Xi Ding<sup>1#</sup>, Jie Zhang<sup>2#</sup>, Di Liu<sup>3</sup>, Wen Xu<sup>4</sup>, De-yi Lu<sup>5</sup>, Li-Ping Zhang<sup>6✉</sup>, Bo Su<sup>7✉</sup>

1. Department of General Surgery, Shanghai Pulmonary Hospital, School of Medicine, Tongji University
2. Department of Oncology, Shanghai Pulmonary Hospital, School of Medicine, Tongji University
3. Department of Thoracic Surgery, Shanghai Pulmonary Hospital, School of Medicine, Tongji University
4. Department of Respiratory Medicine, Shanghai Pulmonary Hospital, School of Medicine, Tongji University
5. Department of Bioengineering, University of Illinois at Chicago
6. Department of Pathology, Shanghai Pulmonary Hospital, School of Medicine, Tongji University
7. Department of Central Laboratory, Shanghai Pulmonary Hospital, School of Medicine, Tongji University

# Equal contribution

✉ Corresponding author: Li-Ping Zhang, Department of Pathology, Shanghai Pulmonary Hospital, School of Medicine, Tongji University, No. 507, Zhengmin Road, Shanghai, 200433, P.R. China. Tel: +86 021 65115006; Email: lipingzhang2002@outlook.com and Bo Su, Department of Central Laboratory, Shanghai Pulmonary Hospital, School of Medicine, Tongji University, No. 507, Zhengmin Road, Shanghai, 200433, P.R. China. Tel: +86 021 65115006; Email: su\_bo\_s@hotmail.com

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## Abstract

Cytokines are vital mediators involved in tumor immunity. We aimed to explore whether the expression levels of IL-1 $\beta$ , TNF- $\alpha$  and IL-6 have impacts on prognosis of SCLC patients. In this study, we concluded 707 non-operable SCLC patients at stage III or IV into this study and analyzed the relationships between interleukins and OS/PFS by cox regression analysis and Kaplan-Meier analysis (log-rank test). As a result, under current standard chemotherapy, SCLC patients with higher IL-6 expression level had a shortened OS compared with those with normal level (HR: 0.381, 95%CI: 0.177-0.822,  $p=0.014$ ). Furthermore, IL-6 expression level contributed mostly to patients without a smoking history. Non-smoking patients with a high IL-6 level showed a 6 months shortened OS than those with normal IL-6 level (10.50 vs 16.90 months,  $p=0.003$  by Log-Rank test in Kaplan-Meier analysis). IL-6 had no obvious impacts on first-line PFS in these SCLC patients. To conclude, IL-6 acts as an independent factor of long-term prognosis of SCLC patients under current therapy.

Key words: small cell lung cancer, cytokine, IL-6, prognosis, tumor immunity

## Introduction

Small cell lung cancer is a subtype of lung cancer with extremely high malignance, which accounts for about 15%. Most patients are diagnosed at advanced stages with a starting subjective symptom caused by tumor metastases[1]. For advanced patients, the median OS is just 8 to 13 months, and the 5-year survival rate is about 5%[2]. For decades, a combination of etoposide and a platinum agent has been a cornerstone in SCLC treatment[3]. Although SCLC is sensitive to primary chemotherapy, the relapse rate is over 80% with a 4 to 5 months' median

OS after the recurrence[2].

Immune system has been widely studied as a key procedure in tumorigenesis. Cancer is thought to develop from transformed cells, and immune system is supposed to identify the new pathogens and then clear the potential cancer-inducing cells[4, 5]. However, tumor cells succeed to escape from immune surveillance without immune activity[4, 6] via different ways, including immunological ignorance and immune escape. Expression immunosuppressive factors is a major strategy in tumor immune escape.

The role of various cytokines has been demonstrated in immunosuppression. For example, TGF- $\beta$  inhibits T cell proliferation by blocking IL-2 secretion[7] to suppress the immune system, and protects tumor cells from identified by immune cells[8]. Researchers also demonstrated that tumor progression can be reduced by TGF- $\beta$  inhibition[9].

Interleukin is a main subtype of cytokines, and is essential in activating and regulating immune cells and mediating the activation, proliferation and differentiation of T cells as well as B cells. Interleukin contributes to tumor diseases in many aspects based on the multiple functions. For examples, IL-1 and IL-1 $\beta$  is involved in tumor progression, clinical outcome and risk of gastric cancer, breast cancer and non-small cell lung cancer [10-15]. IL-6 is reported to be involved in tumor progression of breast cancer[16] in molecular experiments[17] and clinical outcomes[18], and also in prostate cancer[19, 20].

The involvements of interleukin in lung cancer are also explored and reported. In terms of patient-based exploration and analysis, IL-6[21] was found to have an increased expression in NSCLC patients. A lot of interleukins, such as serum levels of IL-2 [22], IL-10[23], IL-8[24], IL-6 [25] were reported to have impacts on patients' prognosis of NSCLC. Only in few researches with small sample size, IL-8 was increased in SCLC patients[26] and IL-2 [27, 28] was reported to act as predictors of prognosis in SCLC.

As is mentioned above, the study of correlation of interleukin in NSCLC is far more than that in SCLC. Despite the reported meanings of interleukin in tumor progression and clinical prognosis of lung cancer, the role of interleukin in SCLC is still a blank due to the lack of supporting evidence from clinical data. Here, we analyzed the expression of three cytokines at the time of diagnosis, including TNF- $\alpha$ , IL-1 $\beta$  and IL-6, to explore whether these interleukins influence the clinical outcome of SCLC patients under current standard chemotherapy.

## Materials and Methods

### Ethical approval

This study was approved by the appropriate Ethics Committees of Shanghai Pulmonary Hospital and the approval number was 2015yxy55. All procedures performed in studies involving human participants 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.

### Study objects

We include 707 patients, who were diagnosed as

SCLC pathologically from January 2012 to January 2016 in Shanghai Pulmonary Hospital, into this study. And all of these patients were at clinical stage III or stage IV without surgical resection history. All patients underwent chemotherapy with etoposide and cisplatin/carboplatin according to the SOC (standard of care) of SCLC.

### ELISA assay And Cytokines reference range

All cytokines were performed using patients' peripheral blood by enzyme-linked immunosorbent assay (ELISA). The ELISA assay was performed following general steps with ELISA kit (SIEMENS, Siemens Healthcare Diagnostics Products Ltd.). The indexes were detected by IMMULITE 1000 Immunoassay System (SIEMENS, Immulite®1000).

All cytokines included into this study were inferred as the value at patients' first diagnosis. And the reference ranges of the selected cytokines, according to the given reference on the manual, were as follows: IL-1 $\beta$ : 0-5pg/ml, TNF- $\alpha$ : 0-8.1pg/ml, IL-6: 0-5.9pg/ml. The value of index was defined as higher one if was beyond the reference range.

### Data collection

The basic clinical data were collected at the entry time, including patients' gender, age, clinical stages, smoking history and relative detection indexes. OS (overall survival) time was calculated from the first treating day to the death date caused by any reason. PFS (progression-free survival) time was calculated from the start date of treatment to the date of objective disease progression. If there's no death/disease progression record, the last follow-up date is used instead.

### Statistical analysis

The statistical analysis was accomplished by SPSS software (version 20.0, SPSS Inc., Chicago, IL). The relationships between clinical features and major indicators and OS/PFS were evaluated by multivariate Cox regression analysis. Factor with a p level <0.05 was considered to have statistically significance. The cumulative death probability on significant index was assessed by Kaplan-Meier analysis (log-rank test).

## Results

### General information of studied cases

The general information of the 707 SCLC cases was listed in Supplementary Table 1. Simply, the study group was consisted of 89.1% female and 71.3% patients had a smoking history. All patients were at advanced clinical stage consisting of 49.4% stage III and 50.6% stage IV, and the average age was about 64

years old. 90.7% patients had the symptom of enlarged mediastinal lymph nodes. In terms of IHC neuroendocrine markers, the positive rate of CGA was 38.6%, 69.3% for SYN, and 81.8% for CD56. In terms of cytokines, 22.0% patients had a higher expression of IL-1 $\beta$  that beyond its normal range, 90.1% for TNF- $\alpha$  and 66.8% for IL-6 at the diagnosis time. All rates reported referred to valid percentages.

**Table 1.** The associations of clinical features and interleukins with median OS in 707 SCLC cases by multivariate Cox regression analysis.

Variables	n(N=707)	mOS(95%CI)	HR(95%CI)	p
<b>GENDER</b>				
male	630	9.20(7.98-10.41)	0.847(0.237-3.026)	0.799
female	77	11.93(8.79-15.07)		
<b>AGE</b>				
≤64	366	10.50(8.69-12.30)	0.673(0.389-1.165)	0.157
>64	341	8.76(6.91-10.61)		
<b>CLINICAL STAGE</b>				
III	349	13.06(10.94-15.19)	0.562(0.316-0.998)	<b>0.049*</b>
IV	358	7.33(5.81-8.48)		
<b>ECOG PS</b>				
0-1	512	10.53(9.14-11.92)	0.656(0.258-1.668)	0.376
2-3	33	5.13(3.45-6.80)		
<b>SMOKING HISTORY</b>				
yes	468	9.36(7.91-10.81)	1.939(0.812-4.628)	0.136
no	188	11.93(9.15-14.71)		
<b>TUMOR LOCATION</b>				
central	618	9.46(8.29-10.63)	2.493(0.972-6.399)	0.057
peripheral	87	9.36(3.60-15.12)		
<b>MEDIASTINAL LYMPH NODES</b>				
enlarged	641	9.40(8.22-10.57)	1.050(0.699-1.578)	0.815
normal	44	10.93(2.97-18.89)		
<b>CGA</b>				
positive	263	6.70(4.98-8.42)	1.463(0.808-2.648)	0.209
negative	418	11.36(7.61-15.12)		
<b>SYN</b>				
positive	487	8.80(7.81-9.78)	1.257(0.664-2.380)	0.483
negative	216	13.36(9.98-16.74)		
<b>CD56</b>				
positive	378	12.56(9.49-15.63)	0.697(0.324-1.503)	0.357
negative	84	16.90(4.20-29.60)		
<b>IL-1<math>\beta</math></b>				
normal	327	10.86(9.00-12.73)	0.894(0.652-1.228)	0.490
higher	92	8.56(4.85-12.27)		
<b>TNF-<math>\alpha</math></b>				
normal	238	9.20(7.17-11.22)	2.041(0.574-7.261)	0.271
higher	112	8.50(6.40-10.59)		
<b>IL-6</b>				
normal	135	13.06(8.24-17.88)	0.381(0.177-0.822)	<b>0.014*</b>
higher	272	10.00(8.18-11.81)		

Note: \* refers to  $p < 0.05$ .

### IL-6 was an independent prognostic factor of OS in 707 non-operated advanced SCLC

We conducted the survival analysis in these 707 SCLC cases by multivariate Cox regression analysis of OS. All of the clinical features, including the three interleukins, were included into the analysis. As a

result, clinical stage and the expression of IL-6 were independent prognostic factors with a  $p$  value  $< 0.05$  (Table 1). Focusing on IL-6, patients with a higher expression level, which means the expression level was beyond the normal range, experienced a 3 months shortened OS compared with those with a normal expression level at the first diagnosis (HR: 0.381, 95%CI: 0.177-0.822,  $p = 0.014$ ) (Table 1 and Figure 1A).

### IL-6 mainly influenced the prognosis of non-smoking SCLC patients

In further exploration, the expression level of IL-6 at the diagnosis time mainly influenced the OS of non-smoking SCLC patient in this study. To be detailed, in all patients with IL-6 examination, 106 patients had no smoking history. In these 106 patients, those who had a higher IL-6 expression level showed a 6 months shortened OS than those with a normal IL-6 level at the diagnosis time (10.50 vs 16.90 months,  $p = 0.003$  by Log-Rank test in Kaplan-Meier analysis). And in another subgroup consisting of smoking patients, there was no obvious difference between median OS of higher and normal IL-6 expression level (10.53 vs 11.30 months,  $p = 0.390$ ) (Figure 1B and 1C).

### IL-6 has no obvious impacts on first-line PFS in non-operated advanced SCLC

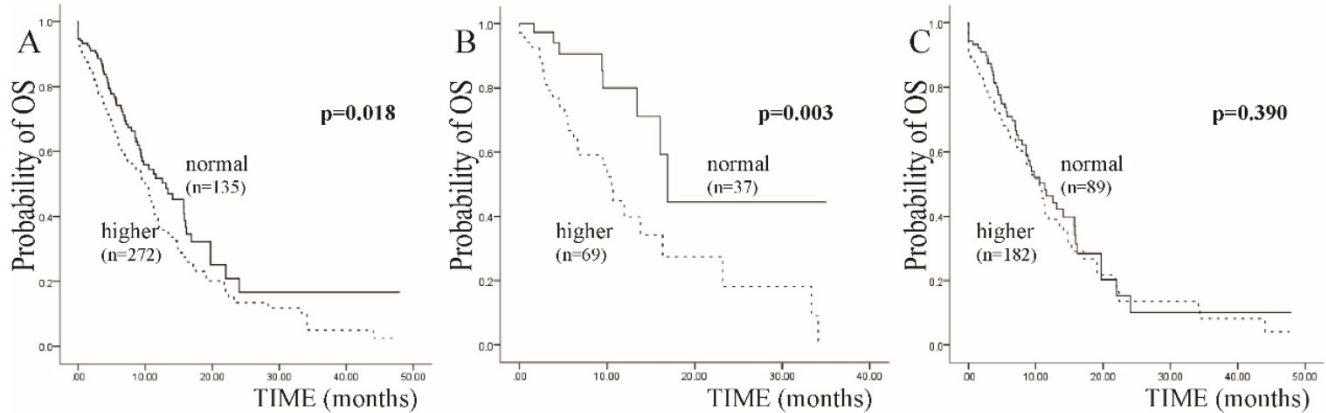
We also conducted the analysis on IL-6 expression level and first-line PFS to explore the correlations. After multivariate Cox regression analysis of all relating factors, only clinical stage acted as independent factors of first-line PFS with a  $p$  value  $< 0.05$ . There was no obvious difference between normal and higher IL-6 groups ( $p = 0.157$ ) (Table 2).

## Discussion

In this study, we found that the plasma IL-6 expression level at diagnosis time had impacts on long-term prognosis of advanced SCLC patients. As is known, IL-6 is a vital cytokine with multiple functions, and the most significant one is the role of STAT3 signaling activator. Through STAT3 signaling pathway, IL-6 plays a positive role in MDSC generation[29].

MDSC (myeloid-derived suppressor cell) was firstly described in cancer patients and murine models decades ago, which includes mature myeloid cells and immature myelo-monocytic precursors. It is demonstrated that MDSC can reduce the proliferation of antigen-specific CD8 $^+$  T cells, increase the apoptosis and dysfunction of T cells, so that lead to immunosuppression. In terms of tumor diseases, the number of MDSCs increases significantly in many kinds of tumors, such as NSCLC and breast cancer. Furthermore, the production of MDSC can impede

effective anti-tumor immunity and reduce the effect of tumor treatment.



**Figure 1.** Kaplan-Meier curves for SCLC patients with IL-6 expression level at diagnosis time. A: In all included SCLC patients. B: In subgroup of non-smoking SCLC patients. C: In subgroup of smoking SCLC patients.

**Table 2.** The associations of clinical features and interleukins with median PFS in 707 SCLC cases by multivariate Cox regression analysis.

Variables	mPFS(95%CI)	HR(95%CI)	p
<b>GENDER</b>			
male	8.60(7.50-9.69)	1.445(0.255-8.186)	0.677
female	8.50(3.67-13.32)		
<b>AGE</b>			
≤64	8.30(7.12-9.48)	2.716(0.989-7.460)	0.053
>64	8.90(7.12-10.67)		
<b>CLINICAL STAGE</b>			
III	10.13(8.65-11.61)	0.330(0.123-0.889)	<b>0.028*</b>
IV	6.36(4.99-7.74)		
<b>ECOG PS</b>			
0-1	8.50(7.20-9.79)	0.097(0.008-1.145)	0.064
2-3	ND		
<b>SMOKING HISTORY</b>			
yes	8.46(7.44-9.48)	1.061(0.313-3.592)	0.924
no	8.20(5.87-10.52)		
<b>TUMOR LOCATION</b>			
central	8.46(7.24-9.68)	1.654(0.468-5.845)	0.435
peripheral	10.76(6.40-15.13)		
<b>MEDIASTINAL LYMPH NODES</b>			
enlarged	8.60(7.27-9.92)	0.630(0.172-2.308)	0.486
normal	8.30(5.52-11.07)		
<b>CGA</b>			
positive	8.96(7.06-10.86)	2.501(0.834-7.497)	0.102
negative	8.16(6.96-9.36)		
<b>SYN</b>			
positive	8.73(7.08-10.38)	2.501(0.834-7.497)	0.102
negative	8.30(6.49-10.10)		
<b>CD56</b>			
positive	8.46(7.72-9.20)	0.470(0.143-1.546)	0.214
negative	6.36(2.84-9.89)		
<b>IL-1β</b>			
normal	8.96(7.43-10.50)	0.991(0.593-1.659)	0.974
higher	8.73(6.54-10.91)		
<b>TNF-α</b>			
normal	7.00(3.34-10.65)	2.339(0.326-16.790)	0.398
higher	9.40(8.21-10.59)		
<b>IL-6</b>			
normal	8.73(6.69-10.76)	1.955(0.772-4.954)	0.157
higher	8.90(7.68-10.11)		

Note: \* refers to p<0.05.

As is reported previously, IL6/STAT3 signaling pathway takes a part in tumor invasion by promoting the gathering and activity of MDSC, including in prostate cancer[30] and breast cancer[31]. Moreover, tumor cells may secrete IL-6 to gather and activate MDSC, and also induce MDSC on self-secretion of IL-6, which induces a positive feedback between tumors and MDSC[32]. Hence, the tumor becomes more aggressive and has a rapid progression. And we can infer that the high expression level of IL-6 also contribute to the malignance the SCLC and lead to the worse clinical outcome by promoting MDSC. What's more, recent studies have shown that some certain anti-tumor regimens, including gemcitabine and sunitinib malate, may eliminate or reverse the production of MDSCs and then improve the therapy efficacy of tumor treatment. And from that, we can get new ideals about future researches on tumor treatment, including SCLC therapy strategy.

We have also taken note of the deficiency of this study. Firstly, the interleukins examined were far too little as compared to the big interleukins family. Secondly, the number of studied SCLC cases was relatively large, but the follow-up time was not long enough, especially for the cases diagnosed in 2015 and 2016. Thirdly, the conclusion would be more convincing and conclusive if validation test or experiment was conducted.

To conclude, we firstly analyzed the relationship between three cytokines, including TNF-α, IL-1β, IL-6, and prognosis of non-operable SCLC patients based on a relatively large sample size. Patients with higher IL-6 expression level showed a shortened OS than those with normal level under current standard SCLC therapy. The impacts were more obvious in patients without smoking history, and in details, higher IL-6 level at diagnosis time led to a 6 months shortened



OS. IL-6 was an independent factor of long-term prognosis in SCLC patients.

## Supplementary Material

Supplementary table 1.

<http://www.jcancer.org/v09p0792s1.pdf>

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## Competing Interests

The authors have declared that no competing interest exists.

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