

Prognostic Significance of Tumor-infiltrating CD8⁺ or CD3⁺ T Lymphocytes and Interleukin-2 Expression in Radically Resected Non-small Cell Lung Cancer

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Abstract

Background: Altered immunoresponse is associated with tumorigenesis and cancer progression. This study assessed the levels of tumor-infiltrating CD3⁺ or CD8⁺ T lymphocytes and interleukin-2 (IL-2) protein in radically resected non-small cell lung cancer (NSCLC) tissues to predict overall survival (OS) of the patients.

Methods: Paraffin-embedded tissue specimens from 129 NSCLC patients were retrospectively collected for immunostaining of CD8⁺, CD3⁺, and IL-2 expression. Clinicopathological and survival data were collected and analyzed using the Chi-squared test, Kaplan–Meier curves, and the log-rank test or the Cox regression model.

Results: The data showed a significant inverse association between CD8⁺ T lymphocyte levels and IL-2 expression ($r = -0.927$; $P = 0.000$) and between the levels of CD8⁺ and CD3⁺ T lymphocytes ($r = -0.722$; $P = 0.000$), but a positive association between CD3⁺ T lymphocyte levels and IL-2 expression ($r = 0.781$; $P = 0.000$) in NSCLC tissues. Furthermore, the levels of CD3⁺ and CD8⁺ T lymphocytes and IL-2 expression were associated with tumor stage ($P = 0.023$, 0.006 , and 0.031 , respectively) and the level of CD8⁺ T lymphocytes was associated with the patient gender ($P = 0.024$). In addition, the levels of CD8⁺ T lymphocytes were associated with an unfavorable 5-year OS, whereas patients with high levels of CD3⁺ T lymphocytes in tumor lesions and IL-2-expressing tumors had significantly better 5-year OS rates than patients with low levels.

Conclusions: The levels of CD8⁺ T cells in tumor lesions and IL-2 expression were both independent predictors of OS for these NSCLC patients. Thus, the detection of tumor-infiltrating CD3⁺ or CD8⁺ T lymphocytes and IL-2 expression could be useful to predict the prognosis of radically resected NSCLC patients.

Key words: Immunohistochemistry; Immunological Parameters; Non-small Cell Lung Cancer; Prognostic Factors

INTRODUCTION

Lung cancer is the leading cause of cancer-related mortality in the world for both men and women.^[1] Histologically, non-small cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancer cases; and to date, most NSCLC patients are still diagnosed at an advanced stage of disease, leading to limited treatment options and a poor 5-year overall survival (OS).^[1] Currently, the tumor, lymph node, metastasis (TNM) staging system is one of the best means to predict survival of NSCLC patients.^[2] Molecularly, different biological factors are involved in NSCLC development and progression; thus, they may serve as biomarkers for prediction of prognosis or treatment responses.

Altered inflammatory and immune responses play a key role in tumor development and progression.^[3] Tumor-associated immune responses are more likely to contribute to tumor progression and immunosuppression than effective antitumor responses, depending on the tissue context and cellular stimuli.^[4] For example, tumor-infiltrating lymphocytes (TILs) are found in a variety of cancer tissues and consist of a significantly higher population of CD3⁺ and CD8⁺ T cells. CD3 is the surface marker of mature T cells and is used to detect T helper and cytotoxic T cells. CD3⁺ T cells have antitumor activity^[5] and TILs and macrophages have a potential dual role in lung cancer by supporting both host-defense and tumor progression. In contrast, CD8⁺ T lymphocytes have cytotoxic activity against cancer cells, and these T cells could play an important role in antitumor immunity. Overall, these immune cells

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produce and release cytokines that modulate the balance between humoral and cell-based immune responses and regulate pro-or antitumor activity in the body. For example, interleukin-2 (IL-2), produced by T cells during an immune response, is necessary for growth, proliferation, and differentiation of T lymphocytes to become effector (such as CD8⁺) or regulatory T cells (T-regs). In this regard, detection of CD3⁺ and CD8⁺ T lymphocytes as well as IL-2 expression in a tumor lesion may help us to predict tumor progression or even the prognosis of patients. In addition, tumor-bearing hosts are frequently in an immunosuppressive state and the function of TILs is impaired due to the unavailability of IL-2 and/or its suppression due to lung cancer cell-derived factors.^[6] IL-2 is mainly secreted by Th1 cells and can induce natural killer (NK) cell proliferation and activity.^[7] A high-dose IL-2 treatment can cause mononuclear macrophage proliferation and differentiation as well as induces mononuclear macrophages to kill tumor cells. IL-2 can also stimulate B cell proliferation and activation. With a high affinity IL-2 receptor expressed in the human body, IL-2 possesses antitumor and antimicrobial activity as well as causes graft rejection and autoimmune responses. For example, Wakabayashi *et al.*^[8] have reported that tumor-infiltrating CD8⁺ T lymphocytes were associated with a shorter OS of NSCLC. Another study^[9] reported that higher numbers of CD8⁺ T cells were associated with better survival of patients with Stage IV NSCLC. In contrast, there was no correlation between CD8⁺ TIL infiltration and the outcome of patients with NSCLC.^[10] Therefore, in this study, we further analyzed the levels of TILs (CD3⁺ or CD8⁺) and IL-2 expression in NSCLC tissues for association with clinicopathological parameters and patient survival.

METHODS

Study population

This study was approved by the Institutional Review Board of The First Affiliated Hospital, Zhengzhou University. We collected tissue specimens from 129 patients who received lung cancer resections between January 2004 and January 2007 in the Department of Thoracic and Cardiovascular Surgery, The First Affiliated Hospital, Zhengzhou University. Patients who received adjuvant radiotherapy or chemotherapy and immunotherapy before surgery were excluded. Patients with squamous cell carcinoma (SCC), adenocarcinoma (AC), adenosquamous carcinoma (ASC), or large cell carcinoma were eligible; but patients with small cell lung cancer, sarcoma, or carcinoma tumors were excluded. All patients were followed up until March 2013 through an outpatient clinic visit and/or telephone interview with family members. The median follow-up time was 36.0 months (ranged between 6 and 109 months). The formalin-fixed, paraffin-embedded tissue blocks were retrieved from the Pathology Department and sectioned for immunohistochemistry. Clinicopathological data were also collected from patient medical records [Table 1] according to the TNM criteria of the Union for International Cancer Control.^[11] The histopathological diagnosis was established

Table 1: Association of CD3⁺ and CD8⁺ T cells and IL-2 expression with clinicopathological features of NSCLC

Variable	CD3 ⁺			CD8 ⁺			IL-2		
	High	Low	P	High	Low	P	High	Low	P
Age (years)									
<60	16	34	0.914	21	29	0.691	30	20	0.707
≥60	26	53		36	43		50	29	
Gender									
Male	29	62	0.095	46	45	0.024	54	37	0.333
Female	18	20		11	27		26	12	
pT stage									
pT1	12	8	0.023	3	17	0.006	18	2	0.031
pT2	26	40		28	38		40	26	
pT3	4	15		10	9		10	9	
pT4	5	19		16	8		12	12	
pN stage									
pN0	27	40	0.476	28	39	0.188	46	21	0.431
pN1	9	12		6	15		12	9	
pN2	8	23		18	13		17	14	
pN3	3	7		5	5		5	5	
pTNM stage									
I	23	25	0.058	17	31	0.169	34	14	0.136
II	11	18		12	17		19	10	
III	13	39		28	24		27	25	
Histology									
SCC	20	41	0.626	32	29	0.136	33	28	0.174
AC	20	28		16	32		32	16	
Others	7	13		9	11		15	5	
Smoking status									
Never	17	31	0.853	17	31	0.123	32	16	0.402
Smoker	30	51		40	41		48	33	

NSCLC: Nonsmall cell lung cancer; SCC: Squamous cell carcinoma; AC: Adenocarcinoma; TNM: Tumor, lymph node, metastasis; IL-2: Interleukin-2.

for each patient according to the World Health Organization guidelines.^[12]

Immunohistochemistry

Tissue sections were deparaffinized in xylene and rehydrated in a series of ethanol solutions and then subjected to antigen retrieval in a microwave using a middle-to-high power setting for 8 minutes, followed by a low-to-high temperature for 5 minutes, and cooled down to room temperature. A rabbit monoclonal anti-human CD3 or anti-human CD8 (recognizing cytotoxic T cells) antibody, a rabbit polyclonal anti-human IL-2 antibody, and a streptavidin-peroxidase-conjugated secondary antibody were obtained from Zhongshan Goldenbridge Biotechnology Co., Ltd. (Beijing, China). Immunostaining was performed according to the manufacturer's instructions. The tissue sections were then briefly counterstained with hematoxylin and mounted with a coverslip and Permount (Zhongshan Goldenbridge Biotechnology Co., Ltd.). Tissue sections with known positivity from previous experiments were used as a positive control, whereas tissue sections incubated with phosphate-buffered saline to replace the first antibody served as a negative control.

The immunostained sections were then assessed by two experienced pathologists (HSM and DHC) without knowledge of patient identification.

To score the immunostaining results, we randomly selected five representative high-power microscopic fields ($\times 400$ magnification) of the tumor nest and stroma per section, counted the numbers of positively stained cells, and photographed the sections with a digital camera (Nikon Eclipse 80i; Tokyo, Japan). The mean percentages of stained cells were counted as 0 (negative), 1 ($\leq 10\%$), 2 (11–50%), 3 (51–80%), and 4 ($> 80\%$). Each tissue section was scored semi-quantitatively as 0 (negative), 1 (weak), 2 (moderate), or 3 (strong) staining intensities. Next, we multiplied them to form an immunohistochemical score (H-score) according to a previous study.^[13] An H-score of 0–4 was considered as low expression, while a score of 5–12 was considered as a high expression.

Statistical analysis

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS, version 12.0; SPSS Inc., Chicago, IL, USA). The OS was calculated from the dates of surgery and death from any cause as the endpoint. For each clinicopathological variable and biological marker, the OS and 95% confidence intervals were calculated using the Kaplan-Meier method and statistically analyzed using the log-rank test. Multivariate analysis of OS was performed using Cox's proportional hazard model. A $P < 0.05$ was considered statistically significant.

RESULTS

Characteristics of patients

These 129 NSCLC patients included 91 males and 38 females with a median age of 61 years old (ranged between 32 and 83 years old). The histology showed that 47.29% of patients had SCC, 37.21% had AC, and 15.5% had others (ASC and large cell carcinoma); while 37.2% of patients had Stage I cancer, 22.4% had Stage II, and 40.3% had Stage III. Eighty-one patients (62.79%) had a history of tobacco smoking, and 92 patients (71.32%) had received adjuvant chemotherapy. The median survival of these patients was 34.0 months, and the 5-year OS rate was 36.4% (i.e. 34.1% for males and 42.1% for females) [Table 1].

Levels of CD3⁺ and CD8⁺ T lymphocytes and interleukin-2 expression in non-small cell lung cancer tissue specimens

Interleukin-2 protein and CD3⁺ and CD8⁺ T cells were present in the cancer stroma and cancer cell nests [Figure 1]. Specifically, 91 of these 129 tumor tissue specimens had CD8⁺ T cells in the cancer nests, with a mean number of 4.65 ± 4.25 CD8⁺ T cells; while 126 of these 129 specimens showed CD8⁺ T cells in the cancer stromal tissues, with a mean number of 57.63 ± 23.71 . Moreover, 88 of these 129 cases had CD3⁺ T cells in the cancer nests, with a mean number of 4.95 ± 10.46 CD3⁺ T cells; and 117 of these 129 cases also showed CD3⁺ T cells in the cancer stromal

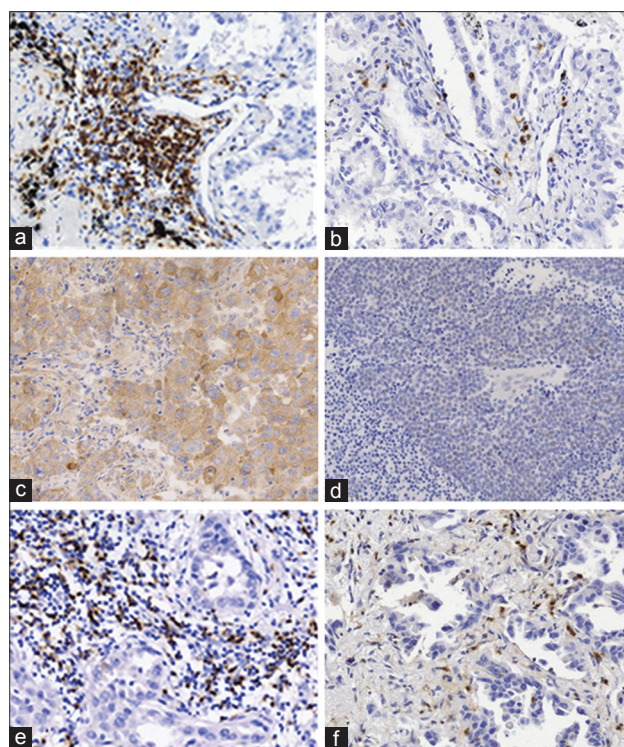


Figure 1: Representative images of immunohistochemically stained non-small cell lung cancer tissue specimens. (a) High levels of CD3⁺ T cell infiltration in the tumor stroma (adenocarcinoma [AC]). (b) Low level of CD3⁺ T cell infiltration in the cancer cell nest and stroma (AC). (c) High level of interleukin-2 (IL-2) expression in the cancer nest (squamous cell carcinoma [SCC]). (d) Low level of IL-2 expression in the cancer nest (SCC). (e) High level of CD8⁺ T cell infiltration within the cancer stroma (AC). (f) Low level of CD8⁺ T cell infiltration within the cancer stroma (AC) ($\times 200$).

tissues, with a mean number of 23.06 ± 21.38 . In addition, IL-2 protein was detected in the cancer cells of 122 NSCLC cases and the cancer stromal cells of 79 cases, with mean numbers of 26.08 ± 21.00 and 2.00 ± 2.04 , respectively.

The number of infiltrating CD3⁺ and CD8⁺ T cells in the cancer stroma was clearly higher than that in the cancer nests ($P = 0.000$), whereas IL-2 protein expression was higher in the cancer nests than in the cancer stroma ($P = 0.000$). There was a significant inverse association ($r = -0.927$; $P = 0.000$) between the number of CD8⁺ T cells and IL-2 protein expression in NSCLC tissues and between the numbers of CD8⁺ T cells and CD3⁺ T cells ($r = -0.722$; $P = 0.000$), whereas there was a positive association between the number of CD3⁺ T cells and IL-2 protein expression ($r = 0.781$; $P = 0.000$) in NSCLC tissue specimens.

Association of CD3⁺ and CD8⁺ T cell levels and interleukin-2 expression with clinicopathological variables from non-small cell lung cancer patients

Next, we associated these parameters with the clinicopathological data and found a significant association between the numbers of CD3⁺ and CD8⁺ T cells and the level of IL-2 expression with tumor stage ($P = 0.023$, 0.006 , and 0.031 , respectively). There was a significant association

between the number of CD8⁺ T cells and the patient gender ($P = 0.024$). However, there was no association between the numbers of CD3⁺ and CD8⁺ T cells or the level of IL-2 expression and gender, age, tumor stage, lymph node or distant metastasis, tobacco smoking, or tumor histology [Table 1].

Association of CD3⁺ and CD8⁺ T cell levels and interleukin-2 expression with survival of these non-small cell lung cancer patients

The survival data from each patient were collected and stratified based on the CD3⁺ and CD8⁺ T cell numbers and IL-2 expression levels [Table 2]. We found that tumor histology was a prognostic factor for these patients (the 5-year OS rates of patients with SCC, AC, or other histological subtypes were 34.4%, 45.8%, and 20.0%, respectively; $P = 0.009$). The same was true for the tumor pathological stage ($P = 0.00001$). However, the patient gender, age, and tobacco smoking status as well as adjuvant chemotherapy treatment had no statistically significant impact on the OS ($P > 0.05$).

Table 2: Univariate and multivariate analyses

Characteristic	Univariate analysis			Multivariate analysis		
	Number of patients	5-year OS (%)	<i>P</i>	HR	95% CI	<i>P</i>
Histology	-	-	0.009	-	-	0.000
SCC	61	34.4	-	1 (Ref)	-	-
AC	48	45.8	-	1.275	0.743–2.186	0.378
Others	20	20.0	-	4.201	2.024–8.721	0.000
pT classification	-	-	0.000	-	-	0.000
T1	20	70.0	-	1 (Ref)	-	-
T2	66	45.5	-	1.201	0.338–2.393	0.833
T3	19	10.5	-	2.280	0.634–8.197	0.207
T4	24	4.2	-	4.974	1.451–17.052	0.011
pN classification	-	-	0.000	-	-	0.042
N0	67	53.7	-	1 (Ref)	-	-
N1	21	33.3	-	1.381	0.608–3.137	0.440
N2	31	12.9	-	4.160	1.341–12.905	0.014
N3	10	0	-	4.508	1.397–14.548	0.012
pTNM stage	-	-	0.000	-	-	0.125
I	48	70.8	-	1 (Ref)	-	-
II	29	24.1	-	1.216	0.327–4.519	0.770
III	52	11.5	-	2.158	0.859–5.418	0.102
CD3	-	-	0.002	-	-	-
Low	82	25.6	-	1 (Ref)	-	-
High	47	55.3	-	1.205	0.642–2.264	0.562
CD8	-	-	0.000	-	-	-
Low	72	48.6	-	1 (Ref)	-	-
High	57	21.1	-	2.154	1.323–3.509	0.002
IL-2	-	-	0.000	-	-	-
Low	49	18.4	-	1 (Ref)	-	-
High	80	47.5	-	1.940	1.104–3.408	0.021

OS: Overall survival; HR: Hazard ratio; *P*: Significance level for log-rank test; 95% CI: 95% confidence interval; Ref.: Reference group; SCC: Squamous cell carcinoma; AC: Adenocarcinoma; TNM: Tumor; lymph node, metastasis; IL-2: Interleukin-2.

Furthermore, the number of CD8⁺ T cells in the tumor lesion appeared to be an unfavorable prognostic factor (5-year OS of 21.1% vs. 48.6% for high vs. low levels; $P = 0.000$, Table 2 and Figure 2b); Table 2 and Figure 2b Patients with high levels of CD3⁺ T cells in the tumor lesions had a significantly better 5-year OS than patients with low levels of CD3⁺ T cells in the tumor lesions (55.3% vs. 25.6%; $P = 0.002$; Table 2 and Figure 2a). Similarly, patients with IL-2-expressing tumors had a better 5-year OS rate than those patients with a low IL-2-expressing tumor (47.5% vs. 18.4%; $P = 0.000$; Table 2 and Figure 2c).

The multivariate analyses showed that tumor histology ($P = 0.000$), tumor stage ($P = 0.000$), TNM ($P = 0.042$), number of CD8⁺ T cells in the tumor lesions ($P = 0.002$), and IL-2 expression levels ($P = 0.021$) were all independent predictors of OS [Table 2].

DISCUSSION

A previous study has demonstrated that TILs contain significantly higher levels of CD8⁺ and CD3⁺ T cells compared to those of peripheral blood.^[14] In this study, we found that IL-2 protein was expressed in tumor and cancer stromal cells and that CD3⁺ T cells and CD8⁺ T cells were present in cancer stromal tissue and in the cancer nest. The number of CD3⁺ and CD8⁺ T cells and IL-2 expression were associated with the NSCLC stage, and the patients with high levels of CD3⁺ T cells in the tumor lesion or with an IL-2-expressing tumor had a significantly better 5-year OS. In contrast, high levels of CD8⁺ T cells were associated with an unfavorable prognosis.

CD8⁺ T cells can recognize tumor-associated antigens as major histocompatibility complex (MHC) class I molecules on the cancer cell surface and can directly lyse cancer cells. Thus, the presence of tumor-infiltrating CD8⁺ T cells is

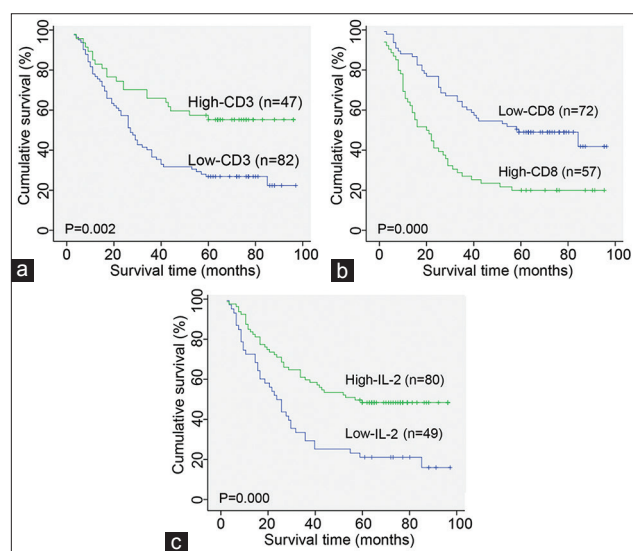


Figure 2: Kaplan–Meier analysis of OS of non-small cell lung cancer patients according to the level of infiltration of CD3⁺ T cells (a) and CD8⁺ T cells (b) as well as interleukin-2 expression (c).

considered as a host immunoreaction against a tumor and is associated with a better prognosis in a variety of cancers.^[15] However, our current study showed that high levels of CD8⁺ T cells in the tumor lesion were associated with a poor prognosis. These data contradict our current knowledge, and the reason is unclear. One possible explanation may be that some immune cells can induce immune tolerance and even promote tumor growth and metastasis, i.e. CD8⁺ T cells *per se* might have diverse functions in a tumor microenvironment;^[16] these cells could lose their antitumor activity after interacting with other B or T lymphocytes through several mechanisms, e.g. escape of immune surveillance due to secretion of immunosuppressive factors (IL-10 and transforming growth factor- β), lack of adequate T-cell costimulation, or downregulation of cell-surface MHC Class II protein expression (immunoediting).^[17] A previous study has shown that nonclassical HLA-G is involved in immune escape mechanisms and could be one of the most powerful molecules for suppression of the innate and/or adaptive immune response in lung and other cancers.^[18] Another possibility may be that CD8⁺ T cells in the tumor nest are associated with survival,^[19] whereas CD8⁺ T cells in the tumor stroma are inversely associated with survival. In this study, the number of CD8⁺ T cells was significantly higher in the stroma than inside the cancer nest. An additional possibility may be that tumor-infiltrating CD8⁺ T cells contain high levels of T-regs in addition to cytotoxic T cells. However, further studies are needed to clarify and confirm our current data.

Furthermore, our current study demonstrated that the levels of CD8⁺ T cells in the tumor microenvironment were associated with the pT stage, suggesting that CD8⁺ T cells are more abundant in the tumor stroma with high cellular growth rates and malignancy potential. These CD8⁺ T cells are anergic but cannot lyse tumor cells. Trojan *et al.*^[20] found that CD8⁺ T cells in the tumor cell nest were inadequately activated and incapable of mounting an antitumor immune effect. Tumor immunology is a very complicated field of research, and a great number of factors affect, interrupt, or interact with the favorable immune activity against tumor cells.

A high number of CD3⁺ T cells have been associated with increased apoptosis in patients with NSCLC.^[21] Al-Shibli *et al.*^[22] also have reported that an increasing number of stromal and cancerous CD3⁺ T cells were associated with a better disease-specific survival and that a high stromal density of CD3⁺ T cells was an independent indicator for survival in patients with NSCLC. Our current univariate analysis showed a significant correlation of CD3⁺ T cell levels with better OS of NSCLC patients, but the Cox multivariate model did not confirm the data. We speculate that mature T cells in the tumor microenvironment have an important role in tumor recurrence but might be affected by the ratio and composition of different T cell subtypes. Similar to CD8⁺ T cells, our current data showed that the presence of CD3⁺ T cells within the tumor microenvironment was positively associated with the pT stage; however,

some CD4⁺ CD25⁺ Treg cells are included in these TILs,^[23] which could suppress immune function. CD3 staining alone cannot identify these T-regs. This may contribute to a lack of association of CD3⁺ T cell levels in a tumor tissue with prognosis.

In addition, IL-2 can activate T cells, NK cells, mononuclear macrophages, and marrow B cells to participate in killing tumor cells. However, activated T cells express the IL-2 receptor for IL-2 binding, leading to cell proliferation. A previous study has shown that IL-2 protein is expressed and detected in all types of lung tumor cells,^[24] including atypical carcinoids, and is inversely associated with the proliferative activity of these tumor cells. An impaired immune defense or suppression of cytokine secretion capacity in cancer patients may have clinical relevance and influence patient survival. In addition, suppression of IL-2 secretion has been significantly associated with reduced survival of NSCLC.^[25] The expression of different cytokines in tumor lesions may be a better predictor for prognosis and reflect antitumor immunity. Indeed, our current study showed that IL-2 was an independent prognostic parameter. An inverse correlation of CD8⁺ T cells with IL-2 expression and CD3⁺ T cells as well as the association of CD3⁺ T cells and IL-2 expression showed the double-edged sword nature of immune factors as well as the complex relationship between them.

However, our current study was just a proof-of-principle study, and much more research is needed because antitumor immunology is very complex and a great number of factors and cells are involved. Future studies will precisely identify the subtypes of lymphocytes in tumor lesions and assess the expression of cytokines and chemokines in NSCLC tissues to better understand their role in NSCLC and develop some of them as biomarkers to predict the prognosis or treatment responses.

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