Original Article

Expression of interleukin-1 (IL-1), IL-6, and tumor necrosis factor-α (TNF-α) in non-small cell lung cancer and its relationship with the occurrence and prognosis of cancer pain

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Background: To analyze the expression of interleukin-1 (IL-1), IL-6, and tumor necrosis factor-α (TNF-α) in non-small cell lung cancer (NSCLC) and its relationship with the occurrence and prognosis of cancer pain.

Methods: A total of 113 NSCLC patients (NSCLC group) in People's Hospital of Pengzhou from March 2019 to March 2020 were enrolled, and 109 healthy volunteers (control group) in the same period were selected. The expression levels of IL-1, IL-6, and TNF-α in different populations and in patients with different degrees of cancer pain were compared. Pearson test was used to analyze the correlation between IL-1, IL-6, TNF-α and cancer pain. Multivariate logistic regression was used to analyze the risk factors affecting the poor prognosis of NSCLC patients. Receiver operating characteristic (ROC) curve was drawn to analyze the predictive value of IL-1, IL-6 and TNF-α for poor prognosis of NSCLC.

Results: The levels of IL-1, IL-6, and TNF-α in the NSCLC group were significantly higher than those in the control group ($P<0.05$). According to the Visual Analogue Scale (VAS) scores, 61 cases were divided into the mild group (VAS ≤3 points) and 52 cases were divided into the severe group (VAS >3 points). The levels of IL-1, IL-6, and TNF-α in the severe group were significantly higher than those in the mild group ($P<0.05$). Multivariate logistic regression analysis showed that clinical stage, lymph node metastasis, differentiation, and IL-1, IL-6, and TNF-α levels were independent risk factors for the poor prognosis of NSCLC patients ($P<0.05$). Age, sex, and tumor diameter were not prognostic risk factors ($P>0.05$). The sensitivity and specificity of IL-1 + IL-6 + TNF-α combined for the prediction of poor prognosis of NSCLC were 81.80% and 71.40%, respectively, while the AUC was 0.846 (95% CI: 0.753–0.929), which was significantly higher than that predicted by IL-1, IL-6, and TNF-α alone ($P<0.05$).

Conclusions: The expression levels of IL-1, IL-6, and TNF-α in NSCLC patients were significantly up-regulated, and were closely related to the occurrence and prognosis of cancer pain in patients.

Keywords: Interleukin-1 (IL-1); tumor necrosis factor-α (TNF-α); non-small cell lung cancer (NSCLC); cancer pain; prognosis

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Introduction

The incidence and mortality of lung cancer are high, while the survival rate remains low. According to relevant data, the 5-year survival rate of lung cancer patients is only 15%. Non-small cell lung cancer (NSCLC) accounts for more than 80% of the total incidence of lung cancer. NSCLC patients are prone to tumor invasion of peripheral blood vessels, which results in distant metastasis and affects the prognosis of patients (1). Therefore, improving the accuracy of early diagnosis has a positive impact on improving the prognosis of patients. Cancer pain is a common symptom affecting the quality of life of patients. Most studies have shown that cancer pain in cancer patients is closely related to the level of cytokines (2). Interleukin-1 (IL-1) is an active inflammatory cytokine and an important member of the interleukin family, which can enhance the host's immune response *in vivo* or *in vitro* (3). IL-6 is a cytokine with extensive biological effects, which is closely related to tumor growth (4). Tumor necrosis factor-α (TNF-α) is a multifunctional inflammatory cytokine which stimulates the release of IL-1β and IL-6 (5). Studies have established animal models found that the implantation of homologous MRMT-1 breast cancer cells in rat bone marrow cavity can induce typical pain behavior changes in rats, and studies have found that with the destruction of cancerous bone and the aggravation of tumor load in rat peripheral blood IL-1, IL-6, TNF-α, prostaglandin E are highly expressed, these factors are released by tumor tissue, resulting in changes in the expression of signal peptide and growth factor. The results show that peripheral nerve pain is sensitive, pain threshold is reduced, and the pain feeling is expanded (6). At present, there are few studies on the relationship between IL-1, IL-6, TNF-α and cancerous pain in NSCLC patients and the prognosis of patients with three-factor joint evaluation. Based on this, this study analyzes the expression of IL-1, IL-6, and TNF-α in NSCLC patients and aims to understand its correlation with cancer pain and the prognosis of NSCLC, so as to provide a reference for clinical diagnosis and treatment. We present the following article in accordance with the STARD reporting checklist (available at https://dx.doi.org/10.21037/apm-21-3471).

Methods

General information

A total of 113 patients with NSCLC (NSCLC group) admitted to People's Hospital of Pengzhou from March 2019 to March 2020 were enrolled, including 69 males and 44 females, aged 40–78 years, with an average age of 53.68±4.16 years. The inclusion criteria were as follows: (I) NSCLC patients diagnosed by clinical pathology; (II) complete clinical data; (III) patients signed informed consent. The exclusion criteria were as follows: (I) Patients with malignant tumors, nephrotic syndrome, tuberculosis, and other diseases; (II) chemoradiotherapy and surgical treatment were performed before admission; (III) patients with other pulmonary diseases; (IV) the expected survival time was less than 3 months. In addition, 109 healthy volunteers (control group) in the same period in our hospital were selected, including 61 males and 48 females, aged 40–78 years old, with an average age of 53.57±4.31 years old. There was no significant difference in general data between the 2 groups, and they were comparable (P>0.05). All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics committee of People's Hospital of Pengzhou (No. 2020010) and informed consent was taken from all the patients.

Study methods

Detection methods of IL-1, IL-6, and TNF-α

Fasting venous blood (3 mL) was obtained from patients the next morning after admission and on the morning of physical examination for participants in the control group. Serum was obtained after centrifugation of the samples at 2,000 r/min for 5 min. IL-1, IL-6, and TNF-α were detected by enzyme-linked immunosorbent assay (ELISA) using the Multiskan Ascent automatic enzyme labelling instrument and IL-1, IL-6, and TNF-α reagents provided by Genzyme company. The assay procedures were performed in accordance with the kit instructions.

Assessment of cancer pain

The Visual Analogue Scale (VAS) was used to evaluate the cancer pain of patients. The total score was 10 points, where 0 was painless, ≤3 was painless or mild pain, and >3 points indicated pain affecting sleep and even strong unbearable pain (7).

Prognostic evaluation

The general data of patients were collected, including age, gender, clinical stage (I–II, III–IV), lymph node metastasis (yes, no), tumor diameter (≥5, <5 cm), differentiation degree

Table 1 Comparison of IL-1, IL-6, and TNF-α levels in different populations ($\bar{x}$±s)

Group	Cases	IL-1 (μg/mL)	IL-6 (ng/mL)	TNF-α (pg/mL)
Control group	109	0.11±0.06	50.11±10.84	21.65±5.06
NSCLC group	113	1.05±0.21	72.77±11.49	46.77±7.25
t	–	44.991	15.103	29.836
P	–	<0.001	<0.001	<0.001

IL, interleukin; TNF-α, tumor necrosis factor-α; NSCLC, non-small cell lung cancer.

Table 2 Comparison of IL-1, IL-6 and TNF-α levels in NSCLC patients with different degrees of cancer pain ($\bar{x}$±s)

Group	Cases	IL-1 (μg/mL)	IL-6 (ng/mL)	TNF-α (pg/mL)
Mild group	61	0.81±0.15	63.26±10.31	38.81±5.76
Severe group	52	1.33±0.27	83.94±12.37	56.11±8.10
t	–	12.893	9.693	13.248
P	–	<0.001	<0.001	<0.001

IL, interleukin; TNF-α, tumor necrosis factor-α; NSCLC, non-small cell lung cancer.

(low differentiation, medium-high differentiation), and IL-1, IL-6, and TNF-α levels. Patients were followed up for 12 months to determine metastasis and death, and patients were divided into a poor prognosis and good prognosis group.

Observation indicators

The levels of IL-1, IL-6, and TNF-α in different groups were compared. The correlations between IL-1, IL-6, and TNF-α levels and VAS scores were analyzed. The predictive value of IL-1, IL-6 and TNF-α on the prognosis of NSCLC was calculated.

Statistical analysis

The data were analyzed by SPSS 20.0 software. Measurement data were expressed as mean ± standard deviation ($\bar{x}$±s) and analyzed by the *t* test. Count data were expressed as rates or constituent ratios and the χ^2 test was used. The correlations between IL-1, IL-6, and TNF-α levels and VAS scores were analyzed by the Pearson test. Multivariate logistic regression analysis was used to analyze the risk factors affecting the poor prognosis of NSCLC patients. A receiver operating characteristic (ROC) curve was generated to analyze the predictive value of IL-1, IL-6, and TNF-α levels for the poor prognosis of NSCLC, and the area under the curve (AUC) was calculated. P<0.05 indicated that the difference was statistically significant.

Results

Comparison of IL-1, IL-6, and TNF-α levels in different populations

The levels of IL-1, IL-6, and TNF-α in the NSCLC group were significantly higher than those in the control group (P<0.05), as shown in *Table 1*.

Comparison of IL-1, IL-6 and TNF-α levels in NSCLC patients with different degrees of cancer pain

According to the VAS score, 61 cases were divided into the mild group (VAS ≤3 points) and 52 cases were divided into the severe group (VAS >3 points). The levels of IL-1, IL-6, and TNF-α in the severe group were significantly higher than those in the mild group, and the difference was statistically significant (P<0.05), as shown in *Table 2*.

Correlations between IL-1, IL-6, and TNF-α levels and VAS scores

Levels of IL-1, IL-6, and TNF-α were positively correlated with VAS scores (P<0.05), as shown in *Table 3* and *Figure 1*.

Analysis of risk factors affecting the poor prognosis of NSCLC patients

According to the follow-up data, 84 patients had good prognosis and 29 patients had poor prognosis. Clinical stage, lymph node metastasis, differentiation, and IL-1, IL-6, and TNF-α levels were the single factors affecting the poor prognosis of NSCLC patients (P<0.05), while age, gender, and tumor diameter were not risk factors influencing the prognosis of patients (P>0.05), as shown in *Table 4*.

Multivariate analysis of poor prognosis in NSCLC patients

Multivariate logistic regression analysis showed that clinical stage, lymph node metastasis, degree of differentiation, and IL-1, IL-6, and TNF-α levels were independent risk factors for the poor prognosis of NSCLC patients (P<0.05), as shown in *Table 5* and *Table 6*.

Table 3 Correlations between IL-1, IL-6, and TNF-**α** levels and VAS scores

Index	VAS	
	r	P
IL-1	0.461	0.002
IL-6	0.699	<0.001
TNF-α	0.618	<0.001

IL, interleukin; TNF-α, tumor necrosis factor-α; VAS, Visual Analogue Scale.

The predictive value of IL-1, IL-6, and TNF-α for the poor prognosis of NSCLC

According to the ROC curve, the sensitivity and specificity of IL-1 + IL-6 + TNF-α combined for the prediction of poor prognosis of NSCLC were 81.80% and 71.40%, respectively, with an AUC of 0.846 (95% CI: 0.753–0.929), which were significantly higher than those predicted by IL-1, IL-6, and TNF-α alone (P<0.05), as shown in *Table 7* and *Figure 2*.

Discussion

The interleukin family is closely related to the occurrence of inflammation in the body. Many studies have also shown that its genotyping is closely related to the occurrence and development of NSCLC (8). IL-1 is an active inflammatory cytokine produced by cells involved in the immune response during the process of antigen presentation or antigen uptake to form antibody complexes. The binding of IL-1 to the corresponding receptor can induce the biological effects of immune cells and increase the body's immune response (9). IL-1 is a multifunctional cytokine in NSCLC pathology and cell physiology, and has gradually become a hot topic in clinical research. In previous studies, IL-1 has been found to play an important role in a variety of tumors, participating in tumor angiogenesis, the secretion of growth factors, and tumor metastasis, and is also closely related to prognosis (6,10). IL-6 is an important member of the interleukin family, and previous studies have shown that IL-6 has an important pro-inflammatory effect in a variety

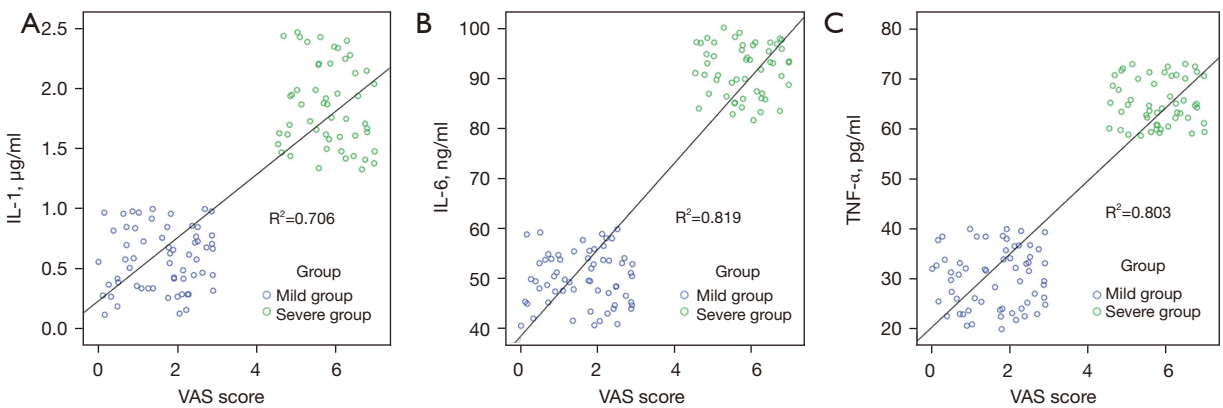

Figure 1 Correlations between IL-1, IL-6, and TNF-α levels and visual analogue scale (VAS) scores. (A) scatter plot of the correlation between IL-1 level and VAS score; (B) scatter plot of the correlation between IL-6 level and VAS score; (C) scatter plot of the correlation between TNF-α level and VAS score. IL, interleukin; TNF-α, tumor necrosis factor-α; VAS, Visual Analogue Scale.

Table 4 Analysis of risk factors affecting the poor prognosis of NSCLC patients

Factor	Good prognosis (n=84)	Poor prognosis (n=29)	χ^2	P
Age (years)			2.442	0.118
≥53	38	18		
<53	46	11		
Gender			2.682	0.101
Male	55	14		
Female	29	15		
Clinical stages			23.278	<0.001
I–II stage	69	10		
III–IV stage	15	19		
Diameter of tumor			0.058	0.809
≥5 cm	50	18		
<5 cm	34	11		
Differentiation degree			5.845	0.015
Poorly differentiated	39	21		
Moderately well differentiated	45	8		
IL-1 (μg/mL)			7.154	0.007
≥1.08	31	19		
<1.08	53	10		
IL-6 (ng/mL)			21.826	<0.001
≥72.77	18	20		
<72.77	66	9		
TNF-α (pg/mL)			9.399	0.002
≥46.77	36	22		
<46.77	48	7		

NSCLC, non-small cell lung cancer; IL, interleukin; TNF-α, tumor necrosis factor-α.

Table 5 Significance and assignment of factors to be analyzed

Factor	Representative meaning	Assignment
X_1	Clinical stages	0= I–II stage; 1= III–IV stage
X_2	Lymph node metastasis	0= No; 1 =Yes
X_3	Differentiation degree	0= Moderately-well differentiated; 1= Poorly differentiated
X_4	IL-1	0= <1.08 (μg/mL); 1= ≥1.08 (μg/mL)
X_5	IL-6	0= <72.77 (ng/mL); 1= ≥72.77 (ng/mL)
X_6	TNF-α	0= <46.77 (pg/mL); 1= ≥46.77 (μg/mL)

IL, interleukin; TNF-α, tumor necrosis factor-α.

Table 6 Multivariate analysis of poor prognosis in NSCLC patients

Factor	Regression coefficient	Standard error	Wald χ^2	P	OR (95% CI)
X_1	0.618	0.144	3.263	0.039	1.855 (1.399–2.460)
X_2	0.567	0.213	4.177	0.010	1.762 (1.612–2.676)
X_3	0.506	0.221	4.692	0.002	1.658 (1.075–2.557)
X_4	0.306	0.117	6.941	<0.001	1.357 (1.079–1.707)
X_5	0.409	0.147	5.069	0.001	1.505 (1.128–2.007)
X_6	0.336	0.118	6.039	<0.001	1.399 (1.110–1.763)

NSCLC, non-small cell lung cancer; OR, odds ratio.

Table 7 Predictive value of IL-1, IL-6, and TNF-α levels for the poor prognosis of NSCLC

Factor	AUC	95% CI	Sensitivity	Specificity
IL-1	0.711	0.617–0.829	0.679	0.592
IL-6	0.736	0.679–0.875	0.698	0.653
TNF-α	0.799	0.733–0.901	0.717	0.677
IL-1 + IL-6 + TNF-α	0.846	0.753–0.929	0.818	0.714

IL, interleukin; TNF-α, tumor necrosis factor-α; NSCLC, non-small cell lung cancer; AUC, area under the curve.

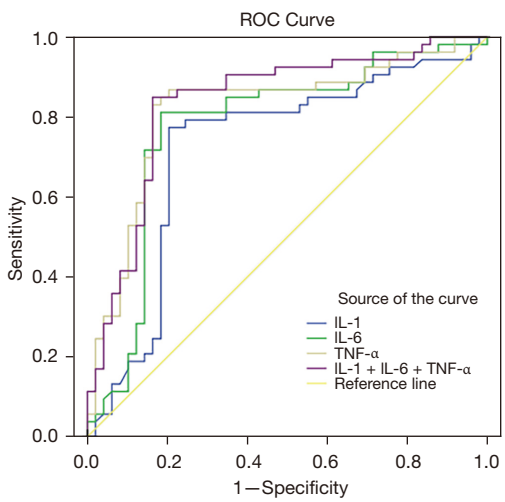

Figure 2 ROC curve of IL-1, IL-6, and TNF-α levels in predicting the poor prognosis of NSCLC. ROC, receiver operating characteristic; IL, interleukin; TNF-α, tumor necrosis factor-α; NSCLC, non-small cell lung cancer.

of inflammatory reactions and diseases (11,12). IL-6 can be secreted by macrophages, fibroblasts, T lymphocytes, and other cells (13). Some studies have found that with the improvement of health, the expression level of IL-6 can be decreased to a certain extent and can gradually return to a healthy level, which may be due to the fact that IL-6 activates T lymphocytes while inducing B lymphocyte differentiation and promotes immunoglobulin secretion (14,15). IL-6 can be self-induced in some tumor cells, thereby promoting the growth of tumor cells (16,17). TNF-α is produced by eosinophils and monocytes, and is a multifunctional inflammatory factor. It can mediate the aggregation of lymphocytes and eosinophils at the inflammatory site and can stimulate the production of IL-6, IL-8, and other factors. It can also inhibit the apoptosis of eosinophils, make eosinophils aggregate and activate, and synthesize fiber cells and colony stimulating factors in the vascular endothelium, so as to promote the persistent inflammatory response of the body (18).

In this study, it was found that the levels of IL-1, IL-6, and TNF-α in NSCLC patients were significantly higher than those in the control group. Combined with the above literature, it was suggested that IL-1, IL-6, and TNF-α were closely related to the development of NSCLC. With the aggravation of cancer pain in patients with NSCLC, the levels of IL-1, IL-6, and TNF-α in the blood of patients also showed a gradual upward trend, and were positively correlated with VAS pain scores. This suggests that the levels of IL-1, IL-6, and TNF-α increased with the increase

of cancer pain intensity, which can provide a reference for the evaluation of cancer pain in patients. In order to prevent cancer pain, it is necessary to strengthen the treatment of tumors, avoid the deterioration of cancer progression, reduce the risk of metastasis and recurrence of tumors, and use analgesic drugs to relieve pain when necessary; patients need active cooperation with doctors. The analysis of risk factors showed that IL-1, IL-6, and TNF-α were independent risk factors for the poor prognosis of NSCLC patients, which was consistent with the results of previous literature (19). An ROC curve was further generated, and it was found that IL-1, IL-6, and TNF-α had a certain value in predicting the prognosis of patients, and the sensitivity and specificity of combined detection were higher than those of the 3 alone, suggesting that the changes in the IL-1, IL-6, and TNF-α levels of patients can provide an important reference for the evaluation of prognosis.

In summary, the expression levels of IL-1, IL-6, and TNF-α in NSCLC patients were significantly up-regulated, which was closely related to the occurrence and prognosis of cancer pain. These findings may provide new ideas for prognosis evaluation and cancer pain treatment.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://dx.doi.org/10.21037/apm-21-3471

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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. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics committee of People's Hospital of Pengzhou (No. 2020010) and informed consent was taken from all the patients.

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