Am J Transl Res 2023;15(3):1871-1879
www.ajtr.org /ISSN:1943-8141/AJTR0147134

Original Article

Expression and clinical significance of tumor necrosis factor receptor-associated factor 1 in peripheral blood of patients with advanced lung cancer

Guojing Li[1], Tiejun Wu[2], Ming Yang[1]

[1]*Department of Cardiothoracic Surgery, Cangzhou Central Hospital, Cangzhou 061001, Hebei, China;*
[2]*Department of Thoracic Surgery, Graduate School of Hebei Medical University, Xingtai Third Hospital, Xingtai 054000, Hebei, China*

Received October 20, 2022; Accepted January 16, 2023; Epub March 15, 2023; Published March 30, 2023

Abstract: Background: To assess the serum level of tumor necrosis factor receptor related factor 1 (TRAF1) in advanced lung cancer patients and its clinical significance. Methods: In this retrospective study, the serum level of TRAF1 in 50 patients with stage III-IV lung cancer and 50 healthy people who received physical examination during the same period were detected and compared. The differences in serum TRAF1 level in patients with lung cancer in terms of gender, age, smoking status, pathological type, tumor location, TNM stage and other clinicopathological features were analyzed. The 50 patients with lung cancer were treated with conventional chemotherapy for 2 cycles, and serum TRAF1 level was tested. The area under the curve (AUC) was calculated to evaluate the diagnostic value of serum TRAF1 for advanced lung cancer. Results: The serum level of TRAF1 in lung cancer patients was significantly higher than that of healthy controls ($P < 0.05$). The serum level of TRAF1 in patients with stage IV lung cancer was significantly higher than that in patients with stage III lung cancer ($P < 0.05$). Serum level of TRAF1 in lung adenocarcinoma and lung squamous cell carcinoma group after chemotherapy was significantly lower than that before chemotherapy ($P < 0.05$); However, the serum level of TRAF1 in small cell lung cancer group after chemotherapy had no significant change compared with that before chemotherapy ($P > 0.05$). The AUC of serum TRAF1 for the diagnosis of lung cancer was 0.903, and the yoden index was 0.668. The best cut-off value of serum TRAF1 for the diagnosis of lung cancer was 113.87 pg/ml, with a sensitivity of 90.6% and a specificity of 78.57%. Conclusion: Serum level of TRAF1 has potential diagnostic value for advanced lung cancer. TRAF1 could assist clinicians to diagnose lung cancer patient and assess patient's condition.

Keywords: Tumor necrosis factor receptor related factor 1, advanced lung cancer, clinical significance

Introduction

Lung cancer is a highly invasive malignant tumor, and its death toll is among the highest in the world for cancer-related diseases. According to the statistics of GLOBOCAN in 2018, the number of lung cancer worldwide accounted for about 1.6% of the total number of cancer cases, and the death toll of lung cancer accounted for about 18.4% of all cancer-related deaths [1]. Due to the occult clinical symptoms and signs of lung cancer, most patients are already in advanced stage when they are diagnosed. According to the histological type, lung cancer is mainly divided into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), and NSCLC mainly includes squamous cell carcinoma (SCC), adenocarcinoma (ADC), etc [2]. At present, the main treatments for lung cancer include surgery, radiotherapy, chemotherapy, targeted therapy and immunotherapy, and the 5-year survival rate remains low (less than 20%) [3]. Therefore, novel specific molecular markers are conducive to the early detection of lung cancer and are of great significance for the targeted treatment of lung cancer while monitoring the therapeutic effect.

Serum tumor markers are important for the development of *in vitro* diagnostic techniques and can be obtained in a cheap and rapid manner [4]. The existing non-invasive diagnostic

methods (including imaging, sputum cytology and bronchoscopy) are difficult to accurately diagnose early stage of lung cancer, so serum tumor markers are an ideal examination method. Serum tumor markers can be used as an auxiliary index to distinguish benign and malignant tumors, assist the clinical staging of tumors, and monitoring their changes can reflect the treatment effect and evaluate the prognosis of patients with cancer [5]. Tumor necrosis factor receptor associated factor (TRAF) family proteins are plasma membrane junction proteins that can directly bind to the intracellular region of cell surface receptors [6]. TRAF family proteins mediate the activation of intracellular signal cascades by regulating the signal transduction pathways of a variety of receptors, including tumor necrosis factor receptors (TNFR), interleukin-1 receptors/toll like receptors (TLR), nod like receptors (NLR) and cytokine receptor family signal pathways [7]. Studies have found that TRAF1 promotes lymphocyte survival in lymphoma by inhibiting apoptosis related signals [8, 9]. In glioblastoma cells, the activation of TRAF1 can inhibit apoptosis and promote cell survival [10]. It was found that the expression level of TRAF1 in nasopharyngeal carcinoma was significantly higher than that in adjacent tissues [11]. Later, another study found that the expression of TRAF1 protein in skin cancer tissues was also upregulated [12]. However, TRAF1 expression was found downregulated in renal cell carcinoma [13]. These results suggest that TRAF1 may play an important role in tumor proliferation and cell survival [8-13]. TRAF1 expression was previously found upregulated in NSCLC tissues [14], but its expression in serum of lung cancer patients was not clear.

In our study, we analyzed the changes of serum TRAF1 level in patients with lung cancer before and after chemotherapy and discussed the relationship between serum TRAF1 level and efficacy of chemotherapy in patients with lung cancer.

Material and methods

Study population

In this retrospective study, the data were retrieved from electronic medical records systems of Cangzhou Central Hospital from January 2019 to January 2021, which included information related to cancer prevalence, incidence, sex, race, histological types, pathological types, survival time, et al. This study was approved and recognized by the ethics committee of Cangzhou Central Hospital.

Inclusion and exclusion criteria

Inclusive criteria: 1) Patients that diagnosed with III-IV stage lung cancer by bronchoscopic biopsy, lymph node puncture, percutaneous lung puncture and cytology; 2) Patients with complete clinical data; 3) Patients with an age ≥ 18; 4) Patients with known serum TRAF1 level.

Exclusion criteria: 1) Patients with more primary carcinomas or secondary tumor; 2) Patients with missing data about survival time or other clinical characteristics; 3) Patients with serious heart, lung, liver, kidney or other important organ diseases and blood system diseases; 4) Patients had received surgery, radiotherapy and other treatment; 5) Patients combined with chronic obstructive pulmonary disease, bronchial asthma and other respiratory diseases or various acute and chronic infections.

Treatment

The SCLC patients received first-line standard chemotherapy: etoposide (H32025583, Jiangsu Hengrui Pharmaceutical Co., Ltd) or irinotecan (100475412, Jiangsu Hengrui Pharmaceutical Co., Ltd) with platinum (15663-27-1, Jiangsu Hengrui Pharmaceutical Co., Ltd). The NSCLC patients, including squamous cell lung carcinoma and lung adenocarcinoma, received a platinum doublet with either carboplatin (15663-27-1, Jiangsu Hengrui Pharmaceutical Co., Ltd) or cisplatin (H37020118, Jiangsu Hengrui Pharmaceutical Co., Ltd) with gemcitabine (100750, Jiangsu Hengrui Pharmaceutical Co., Ltd), vinorelbine (71486-22-1, Jiangsu Hengrui Pharmaceutical Co., Ltd), or taxanes (paclitaxel or docetaxel) (33069-62-4, Jiangsu Hengrui Pharmaceutical Co., Ltd).

Data collection

The basic clinical data of lung cancer patients, including gender, age, smoking status, etc. were collected and recorded. The chest CT results and pathological reports of lung cancer patients before treatment were consulted and

Table 1. Compare characteristics between two groups

	Lung cancer group (n=50)	Healthy control group (n=50)	X^2	*P*
Gender			0.12	0.97
Male	40 (80%)	35 (70%)	-	-
Female	10 (20%)	15 (30%)	-	-
Age (years)	59.88±8.82	58.67±4.93	12.931	0.354
Smoking condition			2.194	0.195
yes	33 (65%)	26 (51.67%)		
no	17 (35%)	24 (48.33%)		
Pathological type			-	-
Adenocarcinoma	26 (52%)	-		
Squamous cell carcinoma	15 (30%)	-		
Non small cell lung cancer	9 (18%)	-		

recorded, as well as the tumor location (left or right lung), pathological type, etc. Then, whether there was lymph node metastasis, brain metastasis or bone metastasis was judged in combination with the results of systemic superficial lymph node ultrasound, PET-CT, systemic bone CT imaging and skull CT or MRI. According to the TNM staging standard of the eighth edition of lung cancer [15], patients with lung cancer were clinically staged.

Enzyme-linked immunosorbent assay (ELISA)

For TRAF1 determination, sera were obtained and stored at -70°C for analysis of TRAF1 at the end of the study. Serum TRAF1 level was measured by ELISA (Cusabio), according to the manufacturer's instructions. The microtiter plate provided in this kit was pre-coated with an antibody specific to TRAF1. Standards or samples were then added to the appropriate microtiter plate wells with a biotin-conjugated polyclonal antibody preparation specific for TRAF1. Next, avidin conjugated to horseradish peroxidase was added to each microplate well and incubated. Then a TMB substrate solution was added to each well. The enzyme-substrate reaction was terminated by the addition of a sulphuric acid solution, and the color change was measured spectrophotometrically at a wavelength of (450±2) nm. The concentration of TRAF1 in the samples was then determined by comparing the O.D. of the samples to a standard curve.

Statistical analysis

All data were analyzed by SPSS 25.0 software. The statistical results were expressed by mean ± standard deviation ($\bar{x}$ ± SD), and the data were compared by t-test. The correlation analysis was conducted by Pearson linear correlation analysis. Analyses were performed using Graph Pad Prism 7 Software (Graph Pad Prism, San Diego, CA). $P < 0.05$ was regarded with statistical difference.

Results

Characteristics between two groups

In our study, there were 50 males and 50 females, and 26 (52%) of them had an adenocarcinoma (LUAD) histology, 25 (30%) had a squamous cell carcinoma histology, 9 (18%) had a NSCLC histology. Furthermore, there was no significant difference in gender, age and smoking status between the lung cancer group and the healthy control group (all $P > 0.05$) (**Table 1**).

Relationship between serum TARF1 level and different clinicopathological features in patients with lung cancer

There was no significant difference in the expression level of serum TRAF1 among patients with different gender, age, smoking status, pathological type, T stage, bone metastasis, brain metastasis or tumor location (all $P > 0.05$) (**Table 2**).

Comparison of serum TRAF1 level between lung cancer patients before chemotherapy and healthy controls

The serum TRAF1 level in the lung cancer patients before chemotherapy was significantly

Table 2. The expression level of serum TARF1 in different clinicopathological characteristics of lung cancer

	group	serum TARF1	X^2	*P*
age			0.333	0.764
	< 65 years old	171±114.93		
	≥ 65 years old	191.31±212.93		
Smoking condition			1.364	0.234
	Yes	188.22±123.67		
	No	155.12±99.98		
Tumor location			2.198	0.278
	Left lung	198.7±143.23		
	Right lung	176.78±150.02		
T stage			4.879	0.054
	T1-2	133.8±70.34		
	T3	162±60.45		
	T4	197.6±109.2		
Bone metastasis			0.098	0.978
	Had	199.98±209.87		
	No	189.67±199.78		
Lymph node metastasis			1.302	0.198
	Had	277.87±120.3		
	No	254±100.09		
Pathological type			1.003	0.188
	Adenocarcinoma	110.23±109.23		
	Squamous cell carcinoma	160.44±142.32		
	Non small cell lung cancer	188.98±101.64		

higher than that in the healthy controls ($P < 0.001$) (**Figure 1**).

Comparison of the serum TRAF1 level between patients with different stages

The serum TRAF1 level in stage IV lung cancer group was significantly higher than that in stage III group ($P < 0.05$) (**Figure 2**).

Comparison of serum TRAF1 level in patients with different pathological types of lung cancer before and after chemotherapy

As shown in **Figure 3A**, the level of serum TRAF1 in patients with lung cancer after 2 cycles of chemotherapy was significantly lower than that before chemotherapy ($P < 0.001$). Furthermore, the serum TRAF1 level in patients with lung adenocarcinoma or lung squamous cell carcinoma after chemotherapy was significantly lower than that before chemotherapy (both $P < 0.01$) (**Figure 3B**, **3C**). However, the serum TRAF1 level in the small cell carcinoma of lung patients after chemotherapy had no significant change compared with that before chemotherapy ($P > 0.05$) (**Figure 3D**).

Diagnostic value of serum TRAF1 level for advanced lung cancer

The AUC of serum TRAF1 for the diagnosis of lung cancer was 0.903 (**Figure 4**), and the Yoden index was 0.668. The best cut-off value of serum TRAF1 for the diagnosis of lung cancer was 113.87pg/ml, with the sensitivity of 90.6% and the specificity of 78.57% (**Table 3**).

Discussion

In this study, we found that the serum level of TRAF1 in patients with lung cancer was significantly higher than that of healthy people, suggesting that the increase of serum TRAF1 level may be related to tumor load and involved in the pathogenesis of lung cancer. The serum level of TRAF1 in patients with TNM stage IV was significantly higher than that in patients

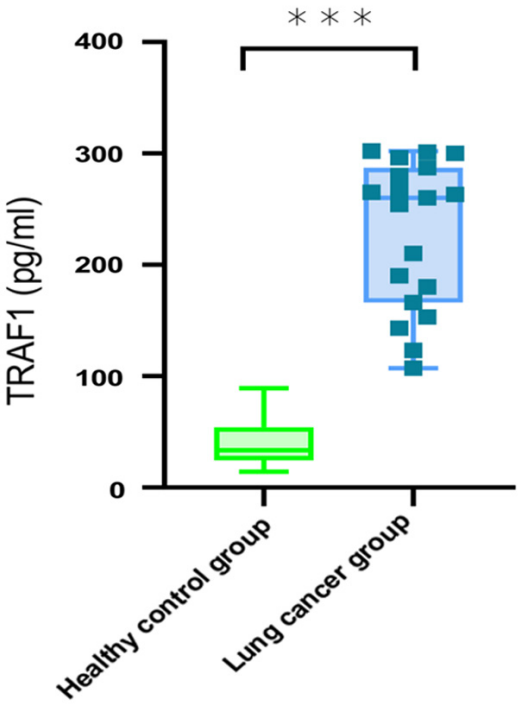

Figure 1. Comparative analysis of serum TRAF1 levels between lung cancer before chemotherapy group and healthy control group. *P < 0.05, **P < 0.01, ***P < 0.001.

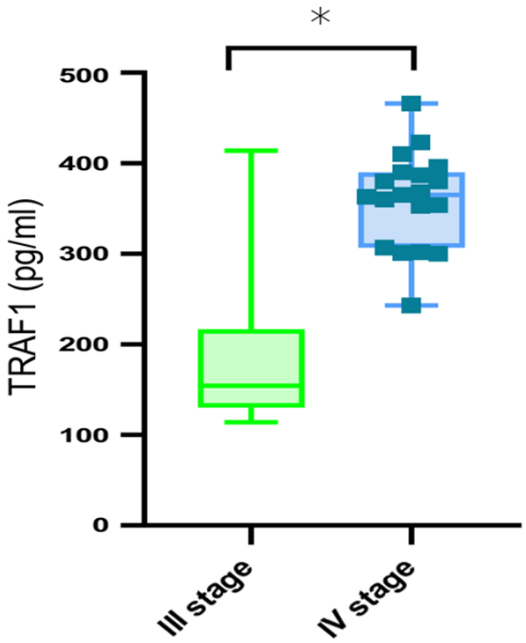

Figure 2. Compare the expression level of serum TRAF1 in patients with different stages of lung cancer. *P < 0.05, **P < 0.01, ***P < 0.001.

with stage III lung cancer, which suggests that the level of serum TRAF1 may be related to the progress of lung cancer, and thus, serum TRAF1 has certain correlation with the clinical staging of lung cancer [15]. There was no significant difference in the expression of TRAF1 in serum between lung cancer patients with bone or brain metastasis. There might be some bias in the results, as the samples included in this study were stage III and stage IV lung cancer patients, and the sample size was too small for patients without lymphatic metastasis. Before chemotherapy, there was no significant difference in the expression level of serum TRAF1 among lung cancer patients with three different pathological types (including lung squamous cell carcinoma, lung adenocarcinoma, and small cell lung cancer), suggesting that the pathological types may not be the influencing factor of serum TRAF1 level in lung cancer patients, or it may be that the sample size included in this study is small. As for the expression level of serum TRAF1 in lung cancer patients with different pathological types before chemotherapy, there was no significant difference, while the level of serum TRAF1 in lung adenocarcinoma after chemotherapy was significantly lower than that in lung squamous cell carcinoma and small cell lung cancer. There was no significant difference in the level of serum TRAF1 between lung squamous cell carcinoma and small cell lung cancer patients. The possible reason is that the chemotherapy regimens of lung cancer patients included in this study were different, and again, it could also be that the sample size was small and led to statistical errors.

In this study, the serum TRAF1 level of lung cancer patients after two cycles of chemotherapy was significantly lower than that before chemotherapy. The significant decrease may be related to the inhibition of tumor growth by chemotherapy, which also suggests that serum TRAF1 may show dynamic changes in the process of chemotherapy. Dynamic monitoring of serum TRAF1 level may be conducive to the evaluation of the condition of lung cancer patients, but whether serum TRAF1 can be used to evaluate the efficacy of chemotherapy in lung cancer patients still needs to be explored and analyzed in multiple chemotherapy cycles [16]. The level of serum TRAF1 in lung adenocarcinoma group and lung squamous cell carcinoma group after chemotherapy was significantly lower than that before chemotherapy, while the serum TRAF1 level in the small cell carcinoma of lung patients

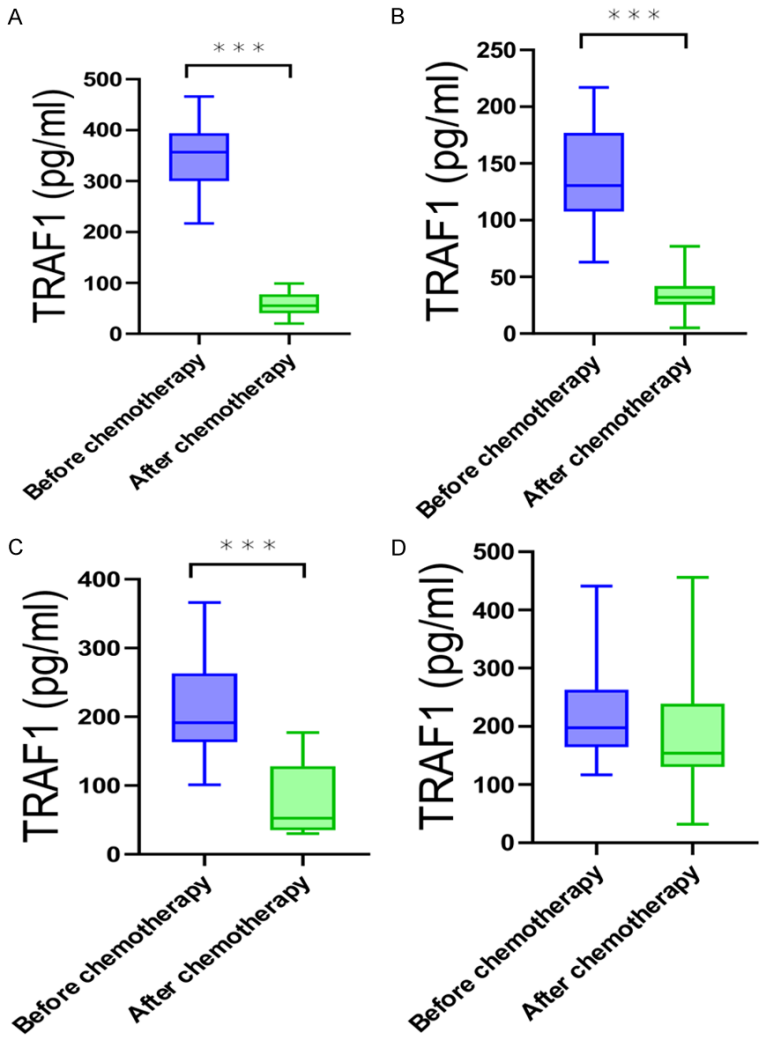

Figure 3. Compare the expression levels of serum TRAF1 in patients with lung cancer before and after chemotherapy and different pathological types. A: Serum TRAF1 in patients with lung cancer before and after chemotherapy; B: Serum TRAF1 in patients with squamous cell carcinoma of lung before and after chemotherapy; C: Serum TRAF1 in patients with adenocarcinoma of lung before and after chemotherapy; D: Serum TRAF1 in patients with small cell carcinoma of lung before and after chemotherapy. *P < 0.05, **P < 0.01, ***P < 0.001.

after chemotherapy had no significant change compared with that before chemotherapy (P > 0.05). The possible reason: (1) It may be related to the characteristics of TRAF1 protein itself [17, 18]. TRAF1 plays different roles in cancer cell survival, apoptosis, cell proliferation, differentiation and inflammation [19-23]. It may have anti-apoptotic effects according to the specific conditions caused by tissue or cell apoptosis [24]. Many studies have found that TRAF1 plays an important role in mediated apoptosis [25-29]. However, other studies have found that the C-terminal of TRAF1, together with TNFR1, negatively regulates TRAF2 [30-33]. (2) Previous studies have shown that tumor cells are heterogeneous, and tumor biological behavior may change after chemotherapy [34]. Serum TRAF1 plays a complex pathophysiological role in the occurrence and development of lung cancer, and the specific mechanism is not clear, so more in-depth research is needed.

TRAF1 has been shown as an important factor for cancer progression [35]. Many researchers have found that TRAF1 is upregulated in blood and tissues of solid tumors, including stomach, ovarian, nasopharyngeal and skin cancers [36-39]. Some studies indicated that TRAF1 is upregulated in the SCLC tissues compared with corresponding non-tumorous lung tissues [41]. Overexpression of TRAF1 also promotes lung cancer cell proliferation, which is consistent with our study.

The limitations of this study were that, this was a retrospective analysis, there might be a selection bias. Additionally, this is a single-center study. Therefore, further large sample RCTs are needed to verify its clinical effect.

Conclusion

In this study, serum TRAF1 has potential diagnostic value for advanced lung cancer, especially in advanced small cell lung cancer. This biomarker could assist clinicians to diagnose lung cancer patient and assess patient's condition.

Disclosure of conflict of interest

None.

Address correspondence to: Ming Yang, Department of Cardiothoracic Surgery, Cangzhou Central Hospital, No. 16 Xinhua West Road, Canal District,

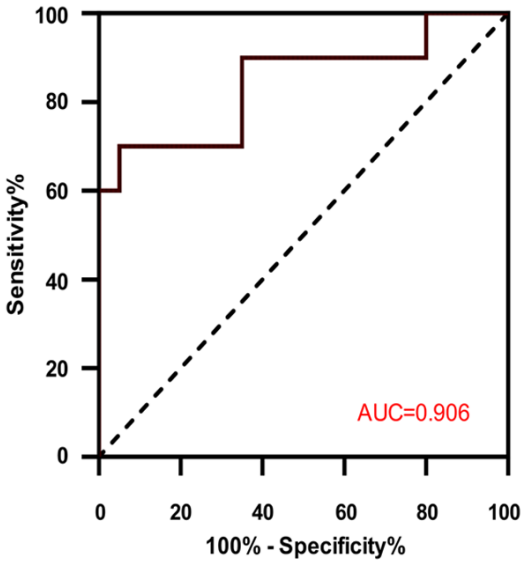

Figure 4. ROC curve of serum TRAF1 in the diagnosis of advanced lung cancer.

Table 3. Optimal cutoff values of serum TRAF1 for lung cancer

Variable	Youden Index	Cutoff value	Sensitivity (%)	Specificity (%)
TRAF1	0.668	113.87	78.57	90.6

Cangzhou 061001, Hebei, China. Tel: +86-159-03175175; E-mail: yangming0212@126.com

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