Original Article

Predictive Value of T-Lymphocyte Subsets in Combination with Serum Tumour Markers for Prognosis of Patients with Non-Small Cell Lung Cancer Undergoing Chemotherapy

(non-small cell lung cancer / T-lymphocyte subset / tumour marker / prognosis / prediction)

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Abstract. We aimed to detect the levels of T-lymphocyte subsets and serum tumour markers in patients with non-small cell lung cancer (NSCLC) before chemotherapy, and to investigate the predictive value of their combined detection for the prognosis of NSCLC patients undergoing chemotherapy. The clinical data of 110 NSCLC patients treated with chemotherapy from January 2019 to February 2021 were analysed retrospectively. All patients were followed up for one year and divided into good prognosis group (surviving cases) and poor prognosis group (deceased cases). The predictive value of T-lymphocyte subsets combined with serum tumour markers for prognosis was analysed. The proportions of patients with tumour-node-metastasis stages III–IV, lymph node metastasis and poor differentiation were higher in the poor prognosis group than those in the good prognosis group ($P < 0.05$). Cox regression analysis revealed that high expression of $CD4^+$ and CEA represented protective factors for poor prognosis of NSCLC patients undergoing chemotherapy [odds ratio (OR) < 1, $P < 0.05$], while high expression of CA125 was a risk factor (OR > 1, $P < 0.05$). All the areas under the receiver operating characteristic curves of single indicator detection ($CD4^+$, CEA and CA125 levels) and their combined detection for prediction of the poor prognosis of NSCLC patients undergoing chemotherapy were > 0.70, which was highest in the case of combined detection. T-lymphocyte subsets and serum tumour markers are closely related to the prognosis of NSCLC patients undergoing chemotherapy, and their combined detection is of high predictive value.

Introduction

Lung cancer is a common malignancy, which ranks first in the incidence and mortality among malignancies in men, and third in the incidence and second in the mortality in women. Non-small cell lung cancer (NSCLC) comprised about 85 % of all lung cancers in 2021 (Fois et al., 2021). Patients with early-stage NSCLC usually have no typical symptoms and the disease has progressed to the middle to late stage by the time they are diagnosed, so the clinical treatment is limited. Duma et al. (2019) reported that NSCLC patients had a 5-year survival rate of about 15.9 %, with a high risk of poor prognosis.

Chemotherapy is an important approach to managing NSCLC, in which carboplatin and pemetrexed are commonly used in clinical practice, with the ability to effectively disrupt the DNA function of tumour cells and suppress tumour cell division, thus controlling the disease condition (Griesinger et al., 2019). Nonetheless, the disease still progresses in some patients undergoing chemotherapy, so their condition is aggravated and the survival time is shortened, posing threats to their life safety. Thus, there is a necessity of identifying the indicators that can efficiently assess the prognosis of NSCLC patients undergoing chemotherapy.

Inhibition of the immune function is the primary cause of disease progression in patients with NSCLC. T lymphocytes are vital indicators of cellular immune function in the case of breast cancer and lung cancer (Kuroda et al., 2021; Qu et al., 2021). Besides, carcinoembryonic antigen (CEA), carbohydrate antigen 125 (CA125) and cytokeratin fragment antigen 21-1 (CYFRA21-1) are commonly used tumour markers for the diagnosis and evaluation of the disease progression in cancer patients. Zheng et al. (2021) reported a high value of tumour markers for diagnosing oesophageal squamous cell carcinoma. However, the predictive val-

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Abbreviations: AUC – area under the curve, CA125 – carbohydrate antigen 125, CD – cluster of differentiation, CEA – carcinoembryonic antigen, CYFRA21-1 – cytokeratin fragment antigen 21-1, NSCLC – non-small cell lung cancer, OR – odds ratio.

ue of T-lymphocyte subsets combined with serum tumour markers for the prognosis of NSCLC patients following chemotherapy has seldom been reported.

Hence, this study aimed to probe into the predictive value of T-lymphocyte subsets combined with serum tumour markers for the prognosis of NSCLC patients undergoing chemotherapy.

Material and Methods

General data

This study was approved by the ethics committee of Yiwu Central Hospital (approval No. YCH201901003), and written informed consent was obtained from all patients. A total of 110 NSCLC patients treated with chemotherapy in our hospital from January 2019 to February 2021 were included in this study, including 73 males and 37 females aged 51–63 years, with a mean age of 57.15 ± 3.18 years. The body mass index (BMI) of the patients was 17–23 kg/m^2, averagely 20.05 ± 2.18 kg/m^2. Patients were classified according to the following criteria: 1) lesion location: central NSCLC in 80 cases and peripheral NSCLC in 30 cases; 2) pathological type: adenocarcinoma in 69 cases, squamous cell carcinoma in 30 cases and others in 11 cases; 3) tumour-node-metastasis (TNM) stage: stages I–II in 69 cases and stages III–IV in 41 cases; 4) differentiation degree: poor differentiation in 49 cases, moderate differentiation in 47 cases and good differentiation in 14 cases.

Inclusion criteria were set as follows: 1) patients who met the diagnostic criteria of NSCLC in the *NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer* and were confirmed by pathological biopsy (Ettinger et al., 2017), 2) those with an expected survival time of more than six months, 3) those with a Karnofsky score higher than 60 points (Mehta et al., 2021), 4) those who received chemotherapy, and 5) those with complete clinical data. Exclusion criteria involved: 1) patients with other lung diseases, 2) those with haematological diseases, 3) those who had recently taken immunosuppressive agents, 4) those with other malignancies, 5) those with acute or chronic infections, or 6) those with severe heart, liver or kidney dysfunction.

Chemotherapy protocol

All patients were given carboplatin (Bristol-Myers Squibb. New York, NY, specification: 15 ml : 150 mg) + pemetrexed (Eli Lilly, Utrecht, Netherlands, specification: 100 mg/vial). Pemetrexed was administered by intravenous drip on day 1 at a dose of 500 mg/m^2 and carboplatin was administered by intravenous drip during the first three days at a dose of 20 mg/m^2 once a day. With 21 days as a course of treatment, the patients were treated for six courses.

Follow-up and grouping criteria

Patients were followed up for one year by outpatient review or telephone contact at one month after chemotherapy and then once every three months. If there was any discomfort, patients should visit the hospital for a timely re-examination. The survival status of patients during the follow-up was recorded, and they were divided into poor prognosis group (deceased cases, with the survival time recorded) and good prognosis group (surviving cases).

Baseline data

Baseline data of patients were recorded, including gender (male/female), age, BMI, lesion location (central/peripheral), pathological type (adenocarcinoma, squamous cell carcinoma, or others), TNM stage (stages I–II or stages III–IV) (Akhurst, 2018), lymph node metastasis (presence/absence), differentiation degree (poor, moderate or well differentiated), smoking, and drinking.

Methods for detection of T-lymphocyte subsets

In the morning before chemotherapy, 5 ml of fasting peripheral elbow venous blood was drawn from each patient and centrifuged at 1.180 × *g* for 6 min. The supernatant was harvested and separated into two test tubes, of which one was used to detect the levels of cluster of differentiation 3 $(CD3)^+$, $CD4^+$ and $CD8^+$ cells by a Navios 6 COLORS/2 LASER flow cytometer (Beckman Coulter, Inc., Clare, Ireland). For cell surface staining, single-cell suspensions (1×10^6) were incubated with fluorophore-conjugated monoclonal antibodies (Thermo Fisher Scientific, Waltham, MA) at room temperature in the dark. For intracellular staining, the cells were stimulated for 4 h at 37 °C in the presence of 5 % CO_2, washed with PBS, fixed, permeabilized, and stained according to the manufacturer's protocol.

Methods for detection of serum tumour markers

The other test tube was taken to detect the levels of CEA, CA125 and CYFRA21-1 by chemiluminescent assay using kits supplied by Fujirebio Diagnostics (Malvern, PA) strictly in accordance with the manufacturer's instructions.

Statistical analysis

SPSS 25.0 software (IBM Inc., Armonk, NY) was utilized for statistical analysis. Measurement data were subjected to the Shapiro-Wilk normality test, and those conforming to normal distribution were expressed as mean ± standard deviation ($\bar{x} \pm s$) and analysed by the independent-samples *t*-test for comparison between groups. Count data were expressed as percentage (%) and analysed using the χ^2 test. The rank sum test was used for comparison of ranked data. Cox regression analysis was employed to analyse the correlations of T-lymphocyte subsets and serum tumour markers with the prognosis of NSCLC patients undergoing chemotherapy. The receiver operating characteristic (ROC) curve was plotted and the area under the curve (AUC) was calculated to evaluate the predictive value of T-lymphocyte subsets combined with serum tumour marker

levels for poor prognosis. $P < 0.05$ was considered statistically significant.

Results

Prognosis of NSCLC patients undergoing chemotherapy

After one year of follow-up, 36 out of the 110 NSCLC patients died after chemotherapy, with a poor prognosis rate of 32.73 % and a survival time of 9.28 ± 2.44 months (Fig. 1).

Baseline data

The proportions of patients with TNM stages III–IV, lymph node metastasis and poor differentiation were higher in the poor prognosis group than those in the good prognosis group ($P < 0.05$). No statistically significant differences were identified in other data between the two groups ($P > 0.05$) (Table 1).

Levels of T-lymphocyte subsets

The $CD4^+$ level in the poor prognosis group was decreased compared with that in the good prognosis group ($P < 0.05$) (Table 2).

Levels of serum tumour markers

The CEA level was lower and the CA15 level was higher in the poor prognosis group than those in the good prognosis group ($P < 0.05$) (Table 3).

Correlations of T-lymphocyte subsets and serum tumour markers with prognosis of NSCLC patients undergoing chemotherapy

The prognosis of NSCLC patients undergoing chemotherapy was set as the dependent variable ("0" = effective and "1" = ineffective), and variables $CD4^+$, CEA and CA125 with statistically significant differences among T-lymphocyte subsets and serum tumour markers between the two groups were selected as the independent variables (continuous variables). Following univariate logistics regression analysis, the eligible factors ($P < 0.1$) were incorporated into the Cox regression analysis. The results manifested that high expressions of $CD4^+$ and CEA were protective factors for poor prognosis of NSCLC patients undergoing chemotherapy [odds ratio (OR) < 1, $P < 0.05$)], while the high expression of CA125 was a risk factor for poor prognosis of NSCLC patients undergoing chemotherapy (OR > 1, $P < 0.05$) (Table 4).

Predictive value of T-lymphocyte subsets combined with serum tumour markers for poor prognosis of NSCLC patients undergoing chemotherapy

The ROC curve was plotted by taking the prognosis of NSCLC patients undergoing chemotherapy as the status variable ("0" = effective and "1" = ineffective) and the levels of T-lymphocyte subset ($CD4^+$) and serum tu-

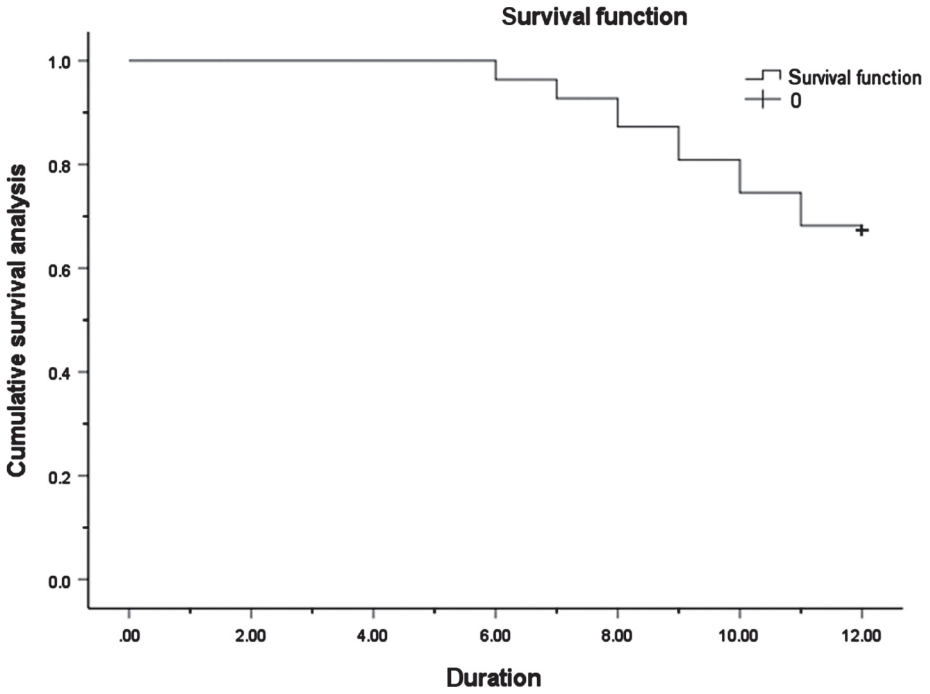

Fig. 1. Survival function of NSCLC patients with poor prognosis after chemotherapy.

Table 1. Baseline data

Group	Gender [N (%)]		Age ($\bar{x} \pm s$, Y)	BMI ($\bar{x} \pm s$, kg/m^2)	Lesion location		Pathological type [N (%)]		
	Male	Female			Central	Peripheral	Adenocarcinoma	Squamous cell carcinoma	Others
Good prognosis (N = 74)	52 (70.27)	22 (29.73)	57.67 ± 6.17	20.19 ± 3.37	51 (68.92)	23 (31.08)	45 (60.81)	21 (28.38)	8 (10.81)
Poor prognosis (N = 36)	21 (58.33)	15 (41.67)	56.09 ± 6.39	19.83 ± 3.02	29 (80.56)	7 (19.44)	24 (66.67)	9 (25.00)	3 (8.33)
$t/\chi^2/Z$	1.546		1.246	0.543	1.653		0.387		
P	0.214		0.215	0.588	0.199		0.824		

Group	TNM stage		Lymph node metastasis		Differentiation degree			Smoking		Drinking	
	I–II	III–IV	Presence	Absence	Poor	Moderate	Good	Yes	No	Yes	No
Good prognosis (N = 74)	52 (70.27)	22 (29.73)	31 (41.89)	43 (58.11)	28 (37.84)	35 (47.30)	11 (14.87)	57 (77.03)	17 (22.97)	46 (62.16)	28 (37.84)
Poor prognosis (N = 36)	17 (47.22)	19 (52.78)	24 (66.67)	12 (33.33)	21 (58.33)	12 (33.33)	3 (8.33)	24 (66.67)	12 (33.33)	20 (55.56)	16 (44.44)
$t/\chi^2/Z$	5.503		5.946		2.001			1.339		0.440	
P	0.019		0.015		0.045			0.247		0.507	

Table 2. Levels of T-lymphocyte subsets ($\bar{x} \pm s$, %)

Group	CD^{3+}	CD^{4+}	CD^{8+}
Good prognosis (N = 74)	52.03 ± 8.84	24.17 ± 4.27	34.82 ± 7.16
Poor prognosis (N = 36)	51.19 ± 9.35	18.64 ± 4.13	36.74 ± 7.32
t	0.459	6.441	1.310
P	0.647	< 0.001	0.193

Table 3. Levels of serum tumour markers ($\bar{x} \pm s$)

Group	CEA/ (ng/ml)	CA125/ (U/ml)	Cyfra21-1/ (ng/ml)
Good prognosis (N = 74)	47.25 ± 5.37	88.36 ± 10.14	32.36 ± 4.19
Poor prognosis (N = 36)	41.58 ± 5.67	107.36 ± 11.16	33.47 ± 4.58
t	5.102	8.921	1.264
P	< 0.001	< 0.001	0.209

Table 4. Correlations of T-lymphocyte subsets and serum tumour markers with prognosis of NSCLC patients undergoing chemotherapy

Influencing factor	B	SE	Wald	P	OR	95% CI
Intercept	–8.924	6.802	1.721	0.190	–	–
$CD4^+$	–0.425	0.148	8.218	0.004	0.654	0.489–0.874
CEA	–0.246	0.102	5.789	0.016	0.782	0.640–0.955
CA125	0.301	0.085	12.652	< 0.001	1.351	1.144–1.594

mour markers (CEA and CA125) in NSCLC patients before chemotherapy as the test variables (Fig. 2). The analysis illustrated that all the AUCs of single indicator detection ($CD4^+$, CEA and CA125 levels) and their combined detection for predicting the poor prognosis of NSCLC patients undergoing chemotherapy were > 0.70, indicating high predictive value, which was the highest by combined detection (Table 5 and Fig. 2).

Discussion

Chemotherapy is currently a principal regimen for treating NSCLC, and pemetrexed combined with carboplatin is commonly used; pemetrexed exerts an anti-folate effect through acting on multiple enzymes in the folate-dependent metabolic pathway, thus restraining tumour metabolism and synthesis and controlling pa-

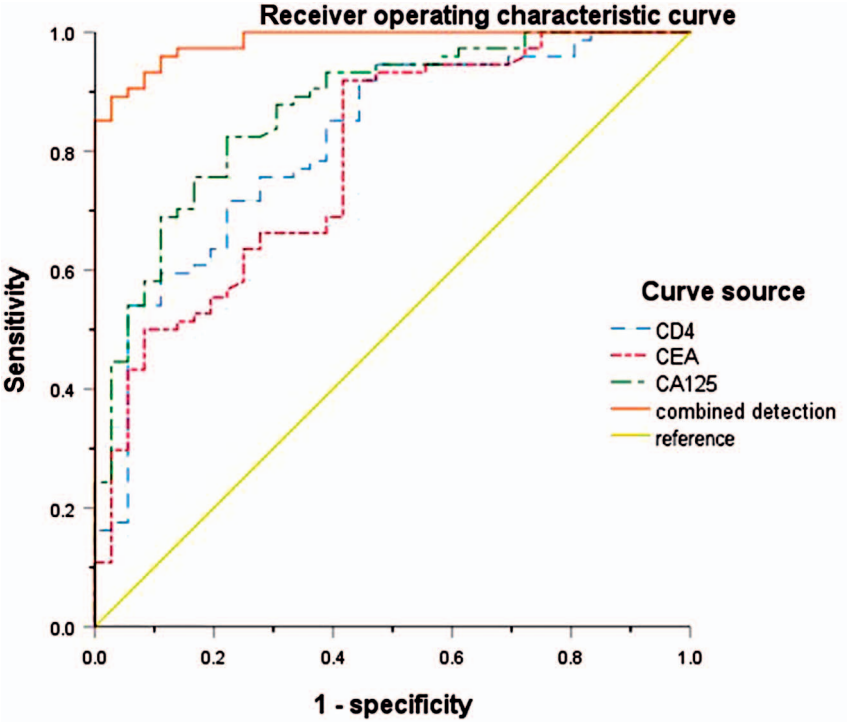

Fig. 2. AUCs of detection of T-lymphocyte subsets combined with serum tumour markers for predicting the poor prognosis of NSCLC patients undergoing chemotherapy.

Table 5. Predictive value of T-lymphocyte subsets combined with serum tumour markers for poor prognosis of NSCLC patients undergoing chemotherapy

Factor	AUC	Cut-off value	95 % CI	P	Specificity	Sensitivity	Youden's index
$CD4^+$	0.816	20.735 %	0.731–0.901	< 0.001	0.722	0.757	0.479
CEA	0.785	40.915 ng/ml	0.694–0.877	< 0.001	0.583	0.917	0.500
CA125	0.870	94.220 U/ml	0.800–0.939	< 0.001	0.778	0.824	0.602
Combined detection	0.984	–	0.968–1.000	< 0.001	0.889	0.959	0.848

tients' disease condition (Horinouchi et al., 2021). Carboplatin is a second-generation platinum-based anti-tumour drug that can bind to tumour DNA to form cross bonds and disrupt DNA function, thus killing tumour cells (Sugawara et al., 2021). Nonetheless, the prognosis is still unsatisfactory in some cases treated with chemotherapy. The results of this study revealed that 36 NSCLC patients died one year after chemotherapy, with a high risk of poor prognosis. Thus, effective prediction of the prognosis of NSCLC patients undergoing chemotherapy and selection of targeted treatment for those with a higher risk of poor prognosis greatly contribute to improving the prognosis and prolonging the survival of patients.

The immune function has been proved to be closely correlated with the progression of malignancies, and cellular immunity functions as a vital player in the anti-tumour immune response (Liu et al., 2021). T-lymphocyte subsets are vital indicators for determining the cellular immune function, and T lymphocytes can influence each other to maintain the balance and normal immune function, but such a balance among T-lymphocyte subsets may be disrupted in the case that the body is stimulated by pathogens, thereby reducing the immune function (Chen et al., 2021). Tumour markers, a class of substances capable of reflecting tumour survival and growth, including proteins, hormones and oncogene products, can be present in the patients' body fluids, cells, or tissues and have a significant role in diagnosing tumours and assessing clinical efficacy (Bodor et al., 2020; Smolle et al., 2020). Yamada et al. (2020) have reported that tumour markers are closely associated with the prognosis of patients undergoing surgery for pancreatic ductal adenocarcinoma. It is thus speculated

that T-lymphocyte subsets and tumour markers are potentially highly associated with the prognosis of NSCLC patients undergoing chemotherapy (Yan et al., 2022).

The results of this study showed that the $CD4^+$ and CEA levels were lower while the CA15 level was higher in the poor prognosis group than those in the good prognosis group. Cox regression analysis revealed that the high expression of $CD4^+$ and CEA served as protective factors and the high expression of CA125 acted as a risk factor for poor prognosis of NSCLC patients undergoing chemotherapy. The results indicated lower levels of $CD4^+$ and CEA as well as a higher level of CA125 in the poor prognosis group, and T-lymphocyte subsets and serum tumour markers were intimately related to the prognosis of NSCLC patients undergoing chemotherapy. The reason is that T lymphocytes are derived from pluripotent stem cells of bone marrow and differentiate and mature under the induction of the thymic hormone. T lymphocytes can be divided into $CD3^+$, $CD4^+$ and $CD8^+$ subsets according to the markers on the membrane of T cells. Among them, $CD4^+$ cells are the linchpin to the human immune system, and they can be divided into T helper 1 and T helper 2 cells, in which T helper 1 cell is able to secrete interleukin 2 (IL-2) that possesses the ability to activate T cells, promote cell inhibition, enhance the body's immune function and stimulate the proliferation of natural killer (NK) cells. Furthermore, NK cells can directly kill tumour cells and diminish the tumour burden in NSCLC patients, thus improving their prognosis (Hu et al., 2021; Xu et al., 2022). $CD8^+$ cells as the most important functional cells of the acquired immunity of the body exert an immunosuppressive effect and have the capability to suppress the toxicity and activity of NK cells, which is an important cause of immunosuppression and tumour cell escape in NSCLC patients. Tumour cells are prone to growth and diffusion in patients with a higher $CD8^+$ level due to the decreased immune function, resulting in poor prognosis (Horton et al., 2021).

CEA, an acidic glycoprotein with human embryonic antigenic determinants, is a non-organic tumour-associated antigen that can be found in the respiratory tract, urinary tract and gastrointestinal tract, belonging to a commonly used tumour markers in clinic (Mishra et al., 2021). Moreover, CEA is also a cell adhesion molecule in the immunoglobulin superfamily, with the effects of homophilic and heterophilic adhesion, thus playing an adhesion role between cancer cells and between cancer cells and stromal collagen, and having close correlations with tumour growth and metastasis (Sun et al., 2020). Relevant studies have demonstrated that CEA may not only cause the accumulation of tumour cells in the microcirculation and thus form tumour thrombi but also prolong the retention time of tumour cells in the vascular bed, thereby elevating the risk of tumour cell metastasis (Jong et al., 2020). Therefore, the risk of tumour cell metastasis is higher in NSCLC patients with a higher level of CEA, which results in disease progression and a poor prognosis. For this reason, T-lymphocyte subsets and serum tumour markers exhibit intimate associations with the prognosis of NSCLC patients undergoing chemotherapy. In addition, the results of this study manifested that all the AUCs of single indicator detection ($CD4^+$, CEA and CA125 levels) and their combined detection for predicting the poor prognosis of NSCLC patients undergoing chemotherapy were > 0.70, indicating high predictive value. Thus, the risk of poor prognosis after chemotherapy can be predicted by detecting T-lymphocyte subsets and serum tumour marker levels of patients before clinical chemotherapy, and targeted interventions should be adopted for high-risk individuals to improve the prognosis and prolong the lives of the patients.

Nevertheless, this study has limits. This is a retrospective study, and there may be potential selection bias. Hence, further prospective studies are still in need to confirm our findings.

In conclusion, T-lymphocyte subsets and serum tumour markers are closely associated with the prognosis of NSCLC patients undergoing chemotherapy, and their combined detection is of high predictive value for the poor prognosis of NSCLC patients treated with chemotherapy. In the future, it is of great clinical significance to test more combinations of T-lymphocyte subsets and serum tumour markers to augment the predictive value.

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