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Original Article

The role of Neutrophil-lymphocyte Ratio (NLR) in predicting tumor prognosis and enlightenment for future treatment of tumor

Jingwei Yao[1,2*], Meiling Wen[1*], Kun Deng[2*], Qiangqiang Xiong[2], Ruimin Zeng[1], Meihong Pan[1], Shanyan Liu[1], Jianhong Zuo[1,2,3]

[1]Gynecology Department, The Affiliated Nanhua Hospital of University of South China, Hengyang 421001, Hunan, P. R. China; [2]Transformation Research Lab, Hunan Province Key Laboratory of Tumor Cellular and Molecular Pathology, Hengyang Medical School, University of South China, Hengyang 421001, Hunan, P. R. China; [3]Clinical Laboratory, The Third Affiliated Hospital of University of South China, Hengyang 421000, Hunan, P. R. China. [*]Co-first authors.

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Abstract: Here we examined the relationship between peripheral leukocytes, Neutrophil-lymphocyte Ratio (NLR) and prognosis in patients with malignant tumor before treatment. In addition, we attempted to find the changes of Neutrophil-lymphocyte Ratio before and after radiotherapy and chemotherapy. We retrospectively conducted an electronic medical record of 453 patients with malignant tumors and compared the leukocytes before treatment between cancer patients and normal people. The leucocyte counts in liver cancer, lung cancer, and laryngeal cancer groups are significantly different from normal group. Kaplan-Meier survival analysis showed that the survival time of low Neutrophil-lymphocyte Ratio group was higher in four kinds of malignant tumors. Chi-square test showed a significant difference in the level of Neutrophil-lymphocyte Ratio in patients with hypersplenism in liver cancer, a significant difference in the level of Neutrophil-lymphocyte Ratio in patients with different tumor stages and tumor diameters in lung cancer, a significant difference in tumor stage in ovarian cancer, a significant difference in classification in laryngeal cancer. Besides, we compared NLR before and after radiotherapy and chemotherapy and we found that the changes of NLR in tumor patients before and after radiotherapy and chemotherapy seemed to be in the opposite trend. Collectively, our study demonstrated that Neutrophil-lymphocyte ratio is related to the survival of the four malignant tumors. Radiotherapy and chemotherapy may have different effects on the change of Neutrophil-lymphocyte Ratio.

Keywords: Leukocyte, Neutrophil-lymphocyte Ratio, malignant tumors, survival, prognosis

Introduction

The high morbidity and mortality of malignant tumors, easy recurrence and early metastasis are the main causes of death at present. Nowadays, medical technology has improved a lot. However, because of people's unhealthy diet, poor living habits and environmental pollution and other factors, the incidence of malignant tumors did not show an ideal downward trend. Although the diagnosis and treatment of malignant tumors have been improved with the improvement of medical technology, the curative effect of malignant tumors in middle and advanced stage is still poor [1, 2].

It has been reported in many studies that inflammation is associated with survival, prognosis and recurrence of malignant tumors [3], such as liver, breast, cervical, laryngeal, ovarian and digestive tract cancers [4, 5]. Tumor can also cause inflammation, leading to up-regulation of cytokines and inflammatory mediators [6]. Neutrophil-lymphocyte Ratio (NLR) may constitute one of the indicators to judge the prognosis of tumor survival. Studies have shown that NLR was related to the prognosis of some malignant tumors [7, 8]. In recent years, cancer immunotherapy has made great progress [9-14]. In order to improve the prognosis of cancer patients, scientists have carried out a

lot of researches [15, 16]. In recent studies, Li. et al. reviewed 509 patients with advanced cancer treated with immune checkpoint inhibitors (ICI), confirming the prognostic value of NLR in the treatment of advanced cancer with ICIS [17]. M. Mendes. et al. retrospectively analyzed 63 patients with non-small cell lung cancer treated with immunotherapy. The results showed that patients with NLR≥5 had a higher risk of disease progression and death compared to those with NLR≤5. NLR could help to predict the response to immunotherapy [18]. This has aroused our interest in the relationship between immune cells and the prognosis of cancer patients. Therefore, the relationship between leukocyte, NLR and prognosis of patients with liver, lung, ovarian and laryngeal cancers has been studied in order to provide a better strategy for clinical treatment of tumors. On the basis of our conclusion that NLR is significantly related to the prognosis of four kinds of cancer patients, we made statistical analysis on some clinicopathological factors that may be related to NLR, and searched for the mechanism of NLR influencing the prognosis. At last, changes in NLR of four kinds of cancer patients before and after radiotherapy and chemotherapy were studied. We tried to investigate the influence of different treatment methods on NLR, so as to provide patients with better options of treatment schemes.

Material and methods

Clinical data

A total of 453 patients with malignant tumors treated in the Affiliated Nanhua Hospital, University of South China and The First Affiliated Hospital Of University Of South China from January 2012 to December 2017 were selected as the study object according to the criteria of the study objects. These patients included 90 patients with liver cancer, 199 patients with lung cancer, 60 patients with laryngeal cancer receiving surgical treatment and 104 patients with ovarian cancer. At the same time, clinical data of 79 healthy volunteers were collected as controls to compare the difference of leukocytes between normal people and cancer patients. All participants in the study signed informed consent, and the experiment was approved by the Ethics Committee.

Research object criteria

Patients with liver cancer, lung cancer, laryngeal cancer and ovarian cancer diagnosed for the first time by clinicopathological examination were selected. There was no second malignant tumor in other parts of the patient except for the primary tumors, and no radiotherapy, chemotherapy and surgical treatment were performed before treatment, and the clinical data were complete. Patients with serious basic diseases such as heart, lung, cerebrovascular and kidney, those with infection, immune diseases and hematological diseases affecting the results of peripheral blood leukocytes, and those with blood transfusion history within 3 months before diagnosis were excluded.

The 90 patients in the liver cancer group were divided into high NLR group and low NLR group, and the median NLR 3.53 was used as the boundary value. There were 44 patients in high NLR group and 46 patients in low NLR group. The 199 patients in the lung cancer group were divided into high NLR group and low NLR group, and the median NLR 3.36 was used as the boundary value. There were 99 patients in high NLR group and 100 patients in low NLR group. The 60 patients in the laryngeal cancer group were divided into high NLR group and low NLR group, and the median NLR 2.80 was used as the boundary value. There were 30 patients in high NLR group and 30 patients in low NLR group. The 104 patients in the ovarian cancer group were divided into high NLR group and low NLR group, and the median NLR 3.54 was used as the boundary value. There were 52 patients in high NLR group and 52 patients in low NLR group. The prognosis of patients in high and low NLR groups was compared.

In the study of the changes in NLR before and after radiotherapy and chemotherapy for four kinds of tumors, because most of the patients with laryngeal cancer underwent radiotherapy and chemotherapy at the same time, the data after radiotherapy and chemotherapy was analyzed. However, most of the patients with ovarian cancer received chemotherapy and rarely received radiotherapy, so we only counted the data of patients with ovarian cancer after chemotherapy. Patients with KPS score less than 70 were excluded.

Collection and grouping of clinicopathological data

In this study, 453 patients with malignant tumors were selected as the research objects, including 90 patients with liver cancer, 199 patients with lung cancer, 60 patients with laryngeal cancer and 104 patients with ovarian cancer, their clinicopathological data were collected for statistical analysis. The data collected include sex, age, tumor size, tumor stage, lymph node metastasis, leukocyte counts before and after radiotherapy and chemotherapy. In addition, some special pathological data, such as HBV infection factors, AFP value in liver cancer, smoking history in lung cancer, were also collected. According to median NLR of tumor patients in each group, each group is further divided into high NLR group and low NLR group.

Follow-up

Patients were followed up regularly after treatment, including regular telephone follow-up, outpatient consultation or in-patient continuing treatment information. The follow-up included inquiring about the patient's survival status, reexamination results, survival time and causes of death. Total survival (OS) is defined as the time from diagnosis to death or the deadline for lost follow-up, and the follow-up ended in December 2018.

Statistical methods

T-test was used to compare the difference between the leukocytes counts in each group and the normal people. In order to study the relationship between leukocyte, NLR and the prognosis of four kinds of cancer patients, univariate analysis was used to analyze the factors that may be related to the prognosis of the four kinds of cancer patients, and statistically significant indicators in univariate analysis were included in the Cox multivariate analysis. In the univariate analysis of lung cancer and ovarian cancer, *P* values of factor "tumor stage" were 0.060 and 0.062 respectively (**Tables 3** and **5**). However, tumor stage is considered to be related to the survival of patients in clinical practice, so the factors are also included in the cox multivariate analysis. Kaplan-Meier survival analysis and Log-rank test were used to draw the survival curves of four patients with malignant tumors after NLR grouping. Chi-square test was used to compare the relationship between the clinicopathological characteristics of patients in each group and the level of NLR. NLR before and after radiotherapy and chemotherapy was analyzed by t-test or rank sum test. SPSS 18.0 and graphpad prism 5.0 were used for statistical analysis. Results with the *p* value less than 0.05 had statistical significance.

Results

Characteristics of factors in four kinds of cancer

90 patients with liver cancer were studied, of which 79 (87.8%) were males. The average age of 90 liver cancer patients was 56.09 years. According to the clinical and pathological factors of the patients, 36 patients (40%) suffered from hypersplenism, 65 patients (72.2%) had tumors over 5 cm in diameter, 16 patients (17.8%) were in T1-T2 stage. According to the treatment, 65 patients (72.2%) received radiotherapy and chemotherapy. The median NLR was 3.53, while the NLR of 46 (51.1%) patients was less than 3.53. 199 patients with lung cancer were studied. The average age of patients was 62 years, including 154 males (77.4%). 63 patients (31.7%) had a history of smoking, 73 patients (36.7%) had tumors with a diameter over 5 cm. According to the classification of lung cancer, 95 patients (47.7%) had squamous cell carcinomas, 77 patients (38.7%) had adenocarcinomas, 19 patients (9.6%) had small cell carcinomas. According to the tumor stage of lung cancer, 14 patients (7.0%) were in stage I-II. According to different treatments, 179 patients (89.9%) received radiotherapy and chemotherapy. The median NLR of 199 lung cancer patients was 3.36, 100 patients (50.2%) with NLR less than 33.36. 60 patients with laryngeal cancer were studied, including 58 males (96.7%). The average age of patients was 60 years. According to the clinicopathological characteristics of the patients, lymph node metastasis occurred in 16 patients (26.7%), 25 patients (41.7%) were in stage I-II. According to the classification of laryngeal cancer, 23 patients (38.3%) were type supraglottic, 32 patients (53.3%) were type glottic, and 5patiens (8.4%) were type subglottic. The median NLR of laryngeal cancer patients was 2.80, 30 patients (50%) with NLR less than 2.80. 104 patients

Table 1. Comparison of leukocyte levels between healthy control group and maligant tumor group

Category	Number of cases	leukocytel values	t value	*p* value
Healthy control group	79	6.471±0.149		
Lung cancer group	199	7.031±0.141	2.304	0.022
Liver cancer group	90	5.704±0.223	2.776	0.006
Ovarian cancer group	104	6.272±0.168	0.86	0.391
Laryngeal cancer group	60	7.523±0.292	3.462	0.001

with ovarian cancer were studied. The average age of the patients was 54 years, of which 20 patients (19.2%) were in stage I-II. According to the classification of ovarian cancer, 68 patients (65.4%) had serous carcinoma of ovary, 21 patients (20.2%) had mucinous carcinoma of ovary. 84 patients (80.8%) received surgical treatment. The median NLR of ovarian cancer patients was 3.54, 52 patients (50%) with NLR less than 3.54.

Univariate analysis

The leucocyte of 453 tumor patients and 79 normal people were compared, the results showed that the leucocyte counts in liver cancer, lung cancer and laryngeal cancer groups were significantly different from those of the normal group (P < 0.05) (**Table 1**). After that, the leucocyte and NLR were included in the univariate analysis of tumor prognosis. At the same time, other factors that may be related to the prognosis of cancer patients were included in the univariate analysis (**Tables 2**-**5**).

The results showed that T staging (P = 0.001), NLR (P = 0.000), radiotherapy and chemotherapy (P = 0.047) were related to the prognosis of liver cancer patients. Radiotherapy and chemotherapy (P = 0.013), neutrophil count (P = 0.038), smoking (P = 0.001) and NLR (P = 0.002) are associate with the survival of lung cancer patients. Tumor stage (P = 0.013) and NLR (P = 0.010) is related to the survival of laryngeal cancer patients, surgery (P = 0.000) and NLR (P = 0.015) are related to the prognosis of ovarian cancer patients.

Figure 1 showed that the survival time of low NLR group was higher than that of high NLR group, and the difference was statistically significant (P < 0.05) (**Figure 1A-D**).

Figure 2 shows that liver cancer patients not received radiotherapy and chemotherapy had a higher risk of death than patients received radiotherapy and chemotherapy (**Figure 2A**), The survival of lung cancer patients without smoking history was better than patients with smoking history (**Figure 2B**). Patients with laryngeal cancer in stage III-IV have a better prognosis than patients in stage I-II (**Figure 2C**).

Multivariate analysis

The results of COX multivariate analysis showed that T staging, NLR, radiation and chemotherapy were associated with the survival of liver cancer patients (P < 0.05). Patients with high NLR had a higher risk of death than patients with low NLR (HR = 2.355, 95% CI = 1.386-4.002, P = 0.002). In lung cancer group, radiation and chemotherapy, smoking were associate with the survival (P < 0.05). Tumor stage and NLR were related the survival of laryngeal cancer patients (P < 0.05). Compared with patients with low NLR, patients with high NLR have a higher risk of death (HR = 2.318, 95% CI = 1.230-4.367, P = 0.009). Surgical treatment is independent prognostic factors for ovarian cancer patients (P < 0.05) (**Tables 6**, **7**). This is consistent with the current clinical situation. For example, patients in the early stage often have better prognosis. High NLR seems to represent poor prognosis of tumor patients, but the mechanism is still unknown. We hypothesize that NLR may have its own independent mechanism for influencing prognosis, or that NLR may change due to changes in pathological factors, thus affecting the prognosis. Will the prognosis of cancer patients be better if NLR changes through treatment? Therefore, two studies have done. On the one hand, the correlation between clinical pathological factors and NLR were studied through statistical analysis. On the other hand, we studied the effect of radiotherapy and chemotherapy on NLR, looking for the difference of NLR between patients before and after radiotherapy and chemotherapy.

Some tumor-related pathological factors are related to the level of NLR

According to the median of NLR, four groups of tumor patients were divided into high NLR group and low NLR group. The number of patients with each clinicopathological data in each group was counted and compared with x^2 test. The results show that there is a significant difference in the level of NLR in patients with

Table 2. 1, 3 & 5 year overall survival of different characteristics and univariate analysis of the relationship between characteristics and liver cancer mortality

	factors	Cases n (%)	1-Year OS (%)	3-Year OS (%)	5-Year OS (%)	X^2	P
Age (years)	< 56	44 (48.9)	0.356	0.105	0.000	3.616	0.057
	≥56	46 (51.1)	0.538	0.242	0.121		
gender	male	79 (87.8)	0.439	0.161	0.054	2.256	0.133
	female	11 (12.2)	0.519	0.260	0.130		
HBV	positive	76 (84.4)	0.472	0.177	0.051	0.242	0.622
	negative	14 (15.6)	0.328	0.164	0.164		
AFP (ng/mL)	< 400	43 (47.8)	0.492	0.239	0.143	2.600	0.107
	≥400	47 (52.2)	0.422	0.121	0.000		
Hypersplenism	YES	36 (40.0)	0.591	0.276	0.110	2.689	0.101
	NO	54 (60.0)	0.363	0.113	0.038		
Diameter (cm)	≤5	25 (27.8)	0.571	0.156	0.052	0.376	0.540
	> 5	65 (72.2)	0.400	0.208	0.083		
T staging	TI-T2	16 (17.8)	0.808	0.314	0.236	11.000	0.001
	T3-T4	74 (82.2)	0.353	0.144	0.000		
Radiation and chemotherapy	YES	65 (72.2)	0.486	0.204	0.076	3.935	0.047
	NO	25 (27.8)	0.342	0.000	0.000		
Leukocyte count (10^9/L)	< 5.41	45 (50.0)	0.559	0.225	0.056	2.247	0.134
	≥5.41	45 (50.0)	0.343	0.125	0.062		
Lymphocyte count (10^9/L)	< 1.09	45 (50.0)	0.485	0.265	0.106	0.678	0.410
	≥1.09	45 (50.0)	0.424	0.109	0.036		
Eosinophil count (10^9/L)	< 0.06	38 (42.2)	0.461	0.193	0.039	0.466	0.495
	≥0.06	52 (57.8)	0.446	0.145	0.097		
Basophil count (10^9/L)	< 0.01	40 (44.4)	0.529	0.178	0.071	0.241	0.624
	≥0.01	50 (55.6)	0.380	0.167	0.056		
Neutrophils/lymphocyte	< 3.53	46 (51.1)	0.637	0.267	0.133	15.951	0.000
	≥3.53	44 (48.9)	0.235	0.067	0.000		

hypersplenism in liver cancer, a significant difference in the level of NLR in patients with different tumor stages and tumor diameters in lung cancer. Besides, the level of NLR in patients with ovarian cancer has a significant difference in tumor stage ($P < 0.05$). In laryngeal cancer, the levels of NLR were significantly different in classification, but there was no significant difference in other clinicopathological data such as sex, age, HBV infection, tumor markers, size and number of tumors (**Tables 8-11**).

Radiotherapy and chemotherapy may have different effects on the change of NLR

The data of four groups of patients who received radiotherapy and chemotherapy was analyzed, The results showed that in the lung cancer group, NLR of the patients receiving chemotherapy decreased significantly compared with that before treatment, while the patients receiving radiotherapy seemed to have the opposite trend, NLR increased after treatment ($P < 0.05$) (**Figure 3B**). Similarly, NLR of the patients in the liver cancer group receiving radiotherapy also increased significantly ($P < 0.05$) (**Figure 3A**). Most laryngeal cancer patients received radiotherapy and chemotherapy at the same time. After radiotherapy and chemotherapy, NLR increased significantly ($P < 0.05$) (**Figure 3C**). In the ovarian cancer group, there was no significant change in NLR before and after chemotherapy ($P = 0.328$) (**Figure 3D**).

Typical case

A patient with Lung Squamous Cell Carcinoma was followed. By collecting her clinical data, a

Table 3. 1, 3 & 5 year overall survival of different characteristics and univariate analysis of the relationship between characteristics and lung cancer mortality

	factors	Cases n (%)	1-Year OS (%)	3-Year OS (%)	5-Year OS (%)	X^2	P
Age (years)	< 62	98 (49.2)	0.827	0.235	0.026	0.908	0.341
	≥62	101 (50.8)	0.812	0.168	0.025		
gender	male	154 (77.4)	0.786	0.188	0.019	1.347	0.246
	female	45 (22.6)	0.933	0.244	0.044		
smoking	NO	136 (68.3)	0.882	0.250	0.029	10.709	0.001
	YES	63 (31.7)	0.683	0.095	0.024		
Diameter (cm)	≤5	126 (63.3)	0.825	0.198	0.029	0.167	0.283
	> 5	73 (36.7)	0.808	0.205	0.021		
Diameter (cm)	Squamous cell carcinomas	95 (47.7)	0.821	0.211	0.016	3.210	0.360
	adenocarcinoma	77 (38.7)	0.844	0.195	0.039		
	small cell carcinoma	19 (9.6)	0.684	0.105	0.053		
	other	8 (4.0)	0.875	0.375	0.000		
Tumor stage	I-II	14 (7.0)	0.929	0.429	0.000	3.547	0.060
	III-IV	185 (93.0)	0.811	0.184	0.027		
treatment	Radiation and chemotherapy	179 (89.9)	0.821	0.212	0.028	6.197	0.013
	Palliative care	20 (10.1)	0.800	0.100	0.000		
leukocyte count (10^9/L)	< 6.99	99 (49.7)	0.798	0.263	0.030	2.958	0.085
	≥6.99	100 (50.3)	0.840	0.140	0.027		
Neutrophil count (10^9/L)	< 4.80	97 (48.7)	0.804	0.268	0.031	4.286	0.038
	≥4.80	102 (51.3)	0.833	0.137	0.026		
Lymphocyte count (10^9/L)	< 1.40	98 (49.2)	0.765	0.184	0.020	0.694	0.405
	≥1.40	101 (50.8)	0.871	0.218	0.040		
Basophil count (10^9/L)	< 0.01	67 (33.7)	0.806	0.179	0.020	0.755	0.385
	≥0.01	132 (66.3)	0.826	0.212	0.028		
Neutrophils/lymphocyte	< 3.36	100 (50.2)	0.870	0.270	0.035	9.781	0.002
	≥3.36	99 (49.8)	0.768	0.131	0.015		

potential relationship between tumor diameter, radiotherapy and chemotherapy and NLR was revealed. In the beginning, CT showed that the tumor size of the patient was about 96 mm * 58 mm (**Figure 4A**) and NLR was 13.8 according to the patient's blood routine. Subsequently, the patient received chemotherapy with docetaxel plus cisplatin. Two months later, the tumor had shrunk to about 63 mm * 38 mm (**Figure 4B**), while NLR also dropped to 4.6, the chemotherapy of docetaxel and cisplatin was continued. Two months later, the tumor shrank again, with a size of 52 mm * 47 mm (**Figure 4C**), and NLR dropped to 4.5. After two rounds of chemotherapy, NLR decreased continuously, the tumor was also shrinking during this time. Half a year later, the patient was hospitalized again. CT showed that the tumor was enlarged, about 82 mm * 43 mm, with pleural effusion (**Figure 4D**). Surprisingly, NLR is also at a high level of 22.25. Afterwards the patients were treated with radiotherapy plus thoracic perfusion chemotherapy. As we expected, the tumor shrank again after 4 months, about 54 mm * 32 mm (**Figure 4E**), and NLR dropped to a lower level of 3.7. After the combined treatment of radiotherapy and chemotherapy, NLR and tumor diameter decreased, which is conducive to the improvement of prognosis.

Discussion

It is universally acknowledged that malignant tumors pose a serious threat to human health and survival [19]. Although the early diagnosis rate of tumors has increased with the improvement of medical level, the survival and prognosis of patients with malignant tumors are still poor. Therefore, it is very important for patients with malignant tumors to seek medical treat-

Table 4. 1, 3 & 5 year overall survival of different characteristics and univariate analysis of the relationship between characteristics and laryngeal cancer mortality

	factors	Cases n (%)	1-Year OS (%)	3-Year OS (%)	5-Year OS (%)	X^2	P
Age (years)	< 60	25 (41.7)	0.918	0.438	0.263	0.136	0.712
	≥60	35 (58.3)	1.000	0.435	0.119		
gender	male	58 (96.7)	0.965	0.434	0.161	0.014	0.906
	female	2 (3.3)	1.000	0.500	0.000		
Lymph node metastases	YES	16 (26.7)	1.000	0.333	0.111	1.485	0.223
	NO	44 (73.3)	0.953	0.471	0.194		
Tumor stage	I-II	25 (41.7)	1.000	0.596	0.309	6.121	0.013
	III-IV	35 (58.3)	0.942	0.318	0.060		
parting	On the glottis type	23 (38.3)	1.000	0.464	0.278	2.714	0.257
	The glottis type	32 (53.3)	0.967	0.421	0.143		
	Subglottic type	5 (8.4)	0.800	0.400	0.000		
leukocyte count (10^9/L)	< 7.48	30 (50.0)	0.966	0.389	0.173	0.960	0.327
	≥7.48	30 (50.0)	0.967	0.482	0.169		
Neutrophil count (10^9/L)	< 4.79	29 (48.3)	1.000	0.387	0.166	0.051	0.822
	≥4.79	31 (51.7)	0.934	0.467	0.175		
Lymphocyte count (10^9/L)	< 1.50	29 (48.3)	1.000	0.446	0.179	0.009	0.926
	≥1.50	31 (51.7)	0.934	0.425	0.177		
Basophil count (10^9/L)	< 0.02	26 (43.3)	0.962	0.402	0.214	0.002	0.968
	≥0.02	34 (56.7)	0.969	0.467	0.146		
Neutrophils/lymphocyte	< 2.80	30 (50.0)	1.000	0.580	0.290	6.625	0.010
	≥2.80	30 (50.0)	0.932	0.311	0.065		

Table 5. 1, 3 & 5 year overall survival of different characteristics and univariate analysis of the relationship between characteristics and ovarian cancer mortality

	factors	Cases n (%)	1-Year OS (%)	3-Year OS (%)	5-Year OS (%)	X^2	P
Age (years)	< 54	48 (46.2)	0.809	0.389	0.195	0.485	0.486
	≥54	56 (53.8)	0.731	0.402	0.131		
CA125 (u/ml)	< 35	14 (13.5)	0.929	0.564	0.226	2.210	0.137
	≥35	90 (86.5)	0.742	0.374	0.141		
Tumor stage	I-II	20 (19.2)	0.950	0.650	0.163	3.494	0.062
	III-IV	84 (80.8)	0.723	0.340	0.177		
parting	Serous adenocarcinoma	68 (65.4)	0.705	0.393	0.119	3.763	0.152
	Mucinous adenocarcinoma	21 (20.2)	0.852	0.374	0.125		
	Other	15 (14.4)	0.933	0.444	0.355		
surgery	YES	84 (80.8)	0.855	0.477	0.192	22.147	0.000
	NO	20 (19.2)	0.400	0.063	0.000		
Neutrophil count (10^9/L)	< 4.23	52 (50.0)	0.885	0.482	0.171	2.796	0.094
	≥4.23	52 (50.0)	0.642	0.311	0.133		
Lymphocyte count (10^9/L)	< 1.21	52 (50.0)	0.692	0.325	0.112	2.977	0.084
	≥1.21	52 (50.0)	0.844	0.476	0.208		
Eosinophilic granulocyte count (10^9/L)	< 0.06	49 (47.1)	0.713	0.325	0.127	0.748	0.387
	≥0.06	54 (52.9)	0.815	0.465	0.181		
Basophil count (10^9/L)	< 0.01	22 (21.2)	0.773	0.409	0.060	0.434	0.510
	≥0.01	82 (78.8)	0.764	0.393	0.180		
Neutrophils/lymphocyte	Low NLR group	52 (50.0)	0.864	0.518	0.215	5.886	0.015
	High NLR group	52 (50.0)	0.669	0.285	0.102		

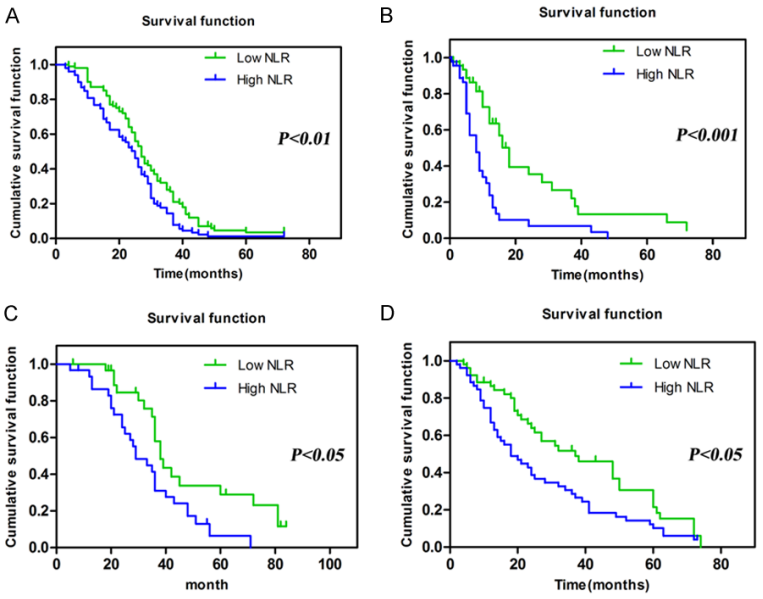

Figure 1. Survival analysis of four malignant tumors in different NLR groups. A. Lung cancer overall survival in high and low NLR groups (P = 0.002). B. Liver cancer overall survival in high and low NLR groups (P = 0.000). C. Laryngeal cancer overall survival in high and low NLR groups (P = 0.01). D. Ovarian cancer overall survival in high and low NLR groups (P = 0.015).

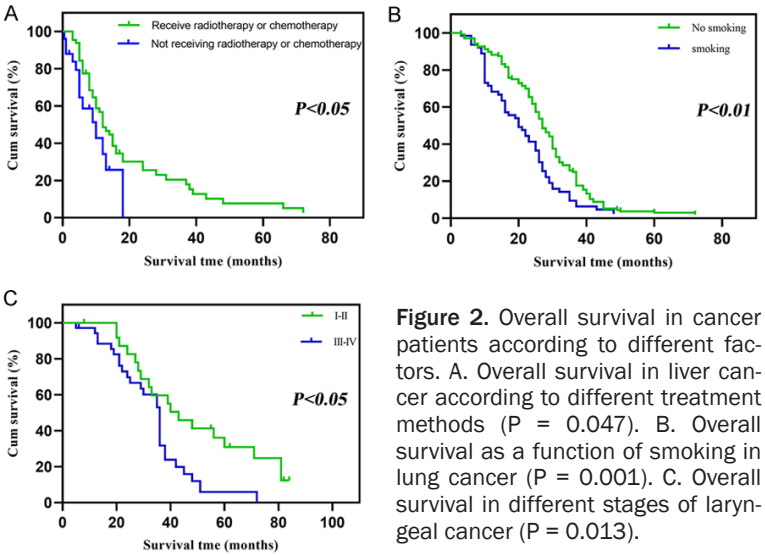

Figure 2. Overall survival in cancer patients according to different factors. A. Overall survival in liver cancer according to different treatment methods (P = 0.047). B. Overall survival as a function of smoking in lung cancer (P = 0.001). C. Overall survival in different stages of laryngeal cancer (P = 0.013).

ment in time and prolong their survival time. At present, the treatment option of cancer is mostly surgery, radiotherapy and chemotherapy. In recent years, immunotherapy seems to bring new expectations to tumor treatment [20, 21]. In this research, on the basis of studying the relationship between leukocyte, NLR and prognosis of four kinds of cancer patients, the relationship between the clinicopathological factors and the level of NLR, the change in NLR before and after radiotherapy and chemotherapy were also studied, hoping to provide assistance for clinical treatment of cancer.

Neutrophil-lymphocyte Ratio (NLR) reflects inflammatory and immune responses of the body. Recent studies have shown that peripheral blood NLR seems to be related to the prognosis of cancer [22-34]. However, whether NLR has the same predictive effect on the prognosis of different tumor patients is rarely studied. In this research, we showed data that NLR is related to the survival of aforementioned four kinds of malignant tumors. The mechanism of NLR affecting the prognosis of cancer patients is still unclear. It may be related to the increase of neutrophil N2 caused by hypoxia [35]. In general, there may be a unique mechanism for NLR to affect the prognosis of patients, or different pathological factors of patients may lead to different NLR of patients, resulting in different prognosis. NLR is only an intermediate parameter, which can predict the prognosis. For example, the immune function of patients with liver cancer complicated with hypersplenism decreases, which may lead to the increase of NLR. The relationship between the clinical pathological factors of four kinds of cancers and the level of NLR was further studied, and the results showed that some pathological factors were significantly related to the level of NLR. NLR before treatment had significant difference in hypersplenism in the patients with liver cancer. In patients with lung cancer and ovarian cancer, NLR before treatment had significant difference in tumor stages ($P < 0.05$). It is also consistent with the current clinical situation. For example, cancer patients in the late stage generally have worse prognosis. However, whether the mechanism of NLR affecting prognosis is related to clinicopatho-

Table 6. COX multivariate analysis of factors affecting the survival of liver cancer and lung cancer patients

	Cox multivariate analysis			
	factors	Hazard ratio	95% CI	P
liver cancer group	NLR			
	Low NLR group	1*	-	-
	High NLR group	2.355	1.386~4.002	0.002
	T staging			
	T1-T2	1*	-	-
	T3-T4	2.608	1.280~5.313	0.008
	Radiation and chemotherapy			
	YES	1*	-	-
	NO	2.064	1.086~3.920	0.027
Lung cancer group	smoking			
	NO	1*	-	-
	YES	1.541	1.110~2.139	0.010
	Tumor stage			
	I-II	1*	-	-
	III-IV	1.584	0.894~2.804	0.115
	Neutrophil count (10^9/L)			
	< 4.80	1*	-	-
	≥4.80	1.037	0.726~1.481	0.841
	Treatment			
	Radiation and chemotherapy	1*	-	-
	Palliative care	1.909	1.184~3.079	0.008
	NLR			
	Low NLR group	1*	-	-
	High NLR group	1.297	0.910~1.847	0.150

*Benchmark of hazard ratio.

Table 7. COX multivariate analysis of factors affecting the survival of laryngeal cancer and ovarian cancer patients

	Cox multivariate analysis			
	factors	Hazard ratio	95% CI	P
laryngeal cancer group	Tumor stage			
	I-II	1*	-	-
	III-IV	2.294	1.202~4.379	0.012
	NLR			
	Low NLR group	1*	-	-
	High NLR group	2.318	1.230~4.367	0.009
ovarian cancer group	Tumor stage			
	I-II	1*	-	-
	III-IV	1.355	0.729~2.516	0.337
	surgery			
	YES	1*	-	-
	NO	2.855	1.598~5.099	0.000
	NLR			
	Low NLR group	1*	-	-
	High NLR group	1.306	0.823~2.072	0.257

*Benchmark of hazard ratio.

Table 8. Comparison of clinicopathological features of liver cancer patients in the high NLR group and the low NLR group

	clinical data	The number of cases	The high NLR group	the low NLR group	X^2	*P* values
gender	male	79	38	41	0.16	0.689
	female	11	6	5		
Age	≥56	46	20	26	1.601	0.206
	< 56	44	25	19		
HBV	positive	76	38	38	0.241	0.623
	negative	14	6	8		
AFP (ng/mL)	≥400	47	26	21	1.68	0.202
	< 400	43	18	25		
Total bilirubin (umol/L)	≥25	26	15	11	1.134	0.287
	< 25	64	29	35		
Hypersplenism	YES	36	13	23	4.63	0.031
	NO	54	32	22		
Tumor diameter (cm)	≥5	65	35	30	2.301	0.129
	< 5	25	9	16		
Portal infiltration	YES	34	19	15	1.07	0.301
	NO	56	25	31		
T staging	T1-T2	16	5	11	2.423	0.120
	T3-T4	74	39	35		
Lymphatic metastasis	YES	16	7	9	0.206	0.650
	NO	74	37	37		

Table 9. Comparison of clinicopathological features of lung cancer patients in the high NLR group and the low NLR group

	clinical data	The number of cases	The high NLR group	the low NLR group	X^2	*P* values
gender	male	154	75	79	0.299	0.585
	female	45	24	21		
Age	≥62	101	48	53	0.406	0.524
	< 62	98	51	47		
Tumor stage	I-II	14	2	12	7.576	0.006
	III-IV	185	97	88		
Diameter (cm)	> 5	73	43	30	3.866	0.049
	≤5	126	56	70		
smoking	YES	63	32	31	0.088	0.766
	NO	136	66	70		
Classification	Lung squamous cell carcinoma	95	47	48	3.116	0.374
	Lung adenocarcinoma	77	42	35		
	Small cell carcinoma of lung	19	8	11		
	other	8	2	6		

logic factors remains to be further studied and it will be helpful for early diagnosis and improvement of prognosis to find out the mechanism of NLR in future research.

On the other hand, NLR is related to the prognosis of 4 kinds of cancer patients, so reducing NLR through various treatment methods may be of great significance for patients. It may be a new field of tumor therapy. Therefore, the changes of NLR in four kinds of tumor patients before and after radiotherapy and chemotherapy were analyzed in this research. The results showed that there were significant differences

Table 10. Comparison of clinicopathological features of laryngeal cancer patients in the high NLR group and the low NLR group

	clinical data	The number of cases	The high NLR group	the low NLR group	X^2	*P* values
gender	male	58	29	29	0.000	1.000
	female	2	1	1		
Age	< 60	25	13	12	0.069	0.793
	≥60	35	17	18		
Tumor stage	I-II	25	14	11	1.526	0.217
	III-IV	35	25	10		
Lymphatic metastasis	YES	16	5	11	3.068	0.080
	NO	44	25	19		
Classification	On the glottis type	23	8	15	7.255	0.027
	The glottis type	32	17	15		
	Subglottic type	5	5	0		

Table 11. Comparison of clinicopathological features of ovarian cancer patients in the high NLR group and the low NLR group

	clinical data	The number of cases	The high NLR group	the low NLR group	X^2	*P* values
Age	≥54	56	31	25	1.393	0.238
	< 54	48	21	27		
Tumor stage	I-II	20	6	14	3.962	0.047
	III-IV	84	46	38		
CA125 (u/ml)	< 35	14	6	8	0.330	0.566
	≥35	90	46	44		
Classification	serous	68	33	35	1.849	0.397
	mucous	21	13	8		
	other	15	6	9		

in the changes of NLR after chemotherapy and radiotherapy, and the changes of NLR after chemotherapy and radiotherapy seemed to show the opposite trend. A typical case was found in our research. NLR of the patients continued to decrease after two rounds of chemotherapy treatments, and the size of the tumor also shrank. Six months later, the tumor was significantly larger and NLR is also at a very high level. We therefore conclude that tumor diameter is significantly related to NLR in patients with lung cancer (**Table 9**). NLR is related to the prognosis of cancer patients and it may decrease after chemotherapy. As we know, radiotherapy and chemotherapy should be able to improve the survival and prognosis of tumor patients, and a large number of reports showed that NLR is likely to be the next indicator to judge the survival and prognosis of tumor. In this research, NLR of lung cancer patients decreased significantly after chemotherapy, while NLR of lung cancer patients and liver cancer patients increased significantly after radiotherapy, which may be related to the sensitivity of different tumors to radiotherapy and chemotherapy, or due to different pathological factors such as tumor stage. At present, the mechanism of NLR influencing the survival and prognosis of tumor is not clear. There is a possibility that the mechanism of radiotherapy to improve the prognosis of patients is not closely related to NLR, but it will lead to the increase of NLR. If the mechanism of action is clear, it will be of great guiding significance for clinical determination of treatments.

As a new tumor therapy, immunotherapy seems to be associated with NLR. Li et al. retrospectively analyzed the clinical data of 92 patients with gastric cancer undergoing radical gastrec-

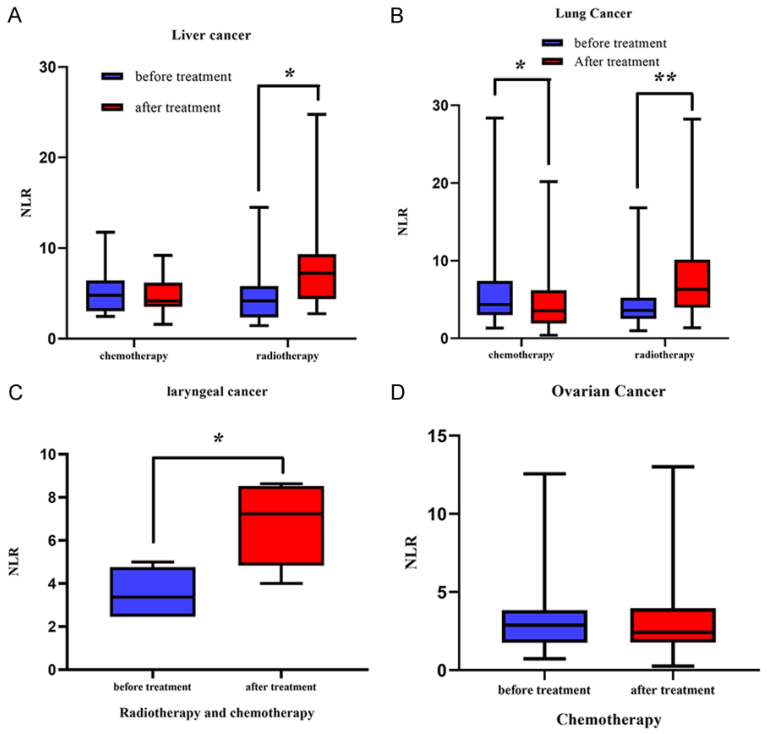

Figure 3. Changes of NLR in four tumor patients before and after radiotherapy and chemotherapy. A. Changes of NLR in liver cancer patients before and after radiotherapy (P = 0.717) and chemotherapy (P = 0.008). B. Changes of NLR in lung cancer patients before and after radiotherapy (P = 0.000) and chemotherapy (P = 0.001). C. Changes of NLR in laryngeal cancer patients before and after radiotherapy and chemotherapy. Patients with laryngeal cancer receive radiotherapy and chemotherapy at the same time. The picture shows the comparison of NLR before and after treatment (P = 0.006). D. Changes of NLR in ovarian cancer patients before and after chemotherapy. Patients with ovarian cancer only received chemotherapy, the figure shows the comparison of NLR before and after chemotherapy (P = 0.328).

tomy. 46 patients who received CIK immunotherapy combined with conventional adjuvant therapy after operation were taken as the experimental group. The preoperative blood cell count, Neutrophil-lymphocyte Ratio (NLR) and Platelet-to-lymphocyte ratio (PLR) were taken as the prognostic indicators. The results showed that low NLR indicated CIK immunotherapy Patients will have more significant benefits, and high NLR indicates that CIK treatment or other more powerful immunotherapy needs more cycles to improve the survival rate of patients [36]. Isabel et al. reviewed 50 patients with non-small cell lung cancer treated with nivolumab and evaluated NLR before treatment. The results showed that most of the patients with low NLR before treatment obtained clinical benefits from nivolumab, while most of the patients with high NLR did not [37].

In this research, we hope to provide new ideas for clinical treatment of cancer through the research on leucocyte and NLR. However, for the current research, the assistance that the research can provide for immunotherapy is still unknown and further research is needed. In this research, the relationship between some cancer-related pathological factors and the level of NLR has been studied and some progress has been made, but the mechanism of the relationship between NLR and cancer prognosis needs further research. In addition, we only studied the changes of NLR before and after radiotherapy and chemotherapy in this research, we may further study the changes of NLR in cancer patients after other treatments, such as surgery and immunotherapy.

Moreover, NLR can be obtained in an economical and convenient way. If the mechanism of NLR affecting prognosis and the relationship between various treatment methods and NLR can be further clarified, it will provide great convenience for the diagnosis, treatment and prognosis evaluation of malignant tumors, and also help most cancer patients prolong their survival time.

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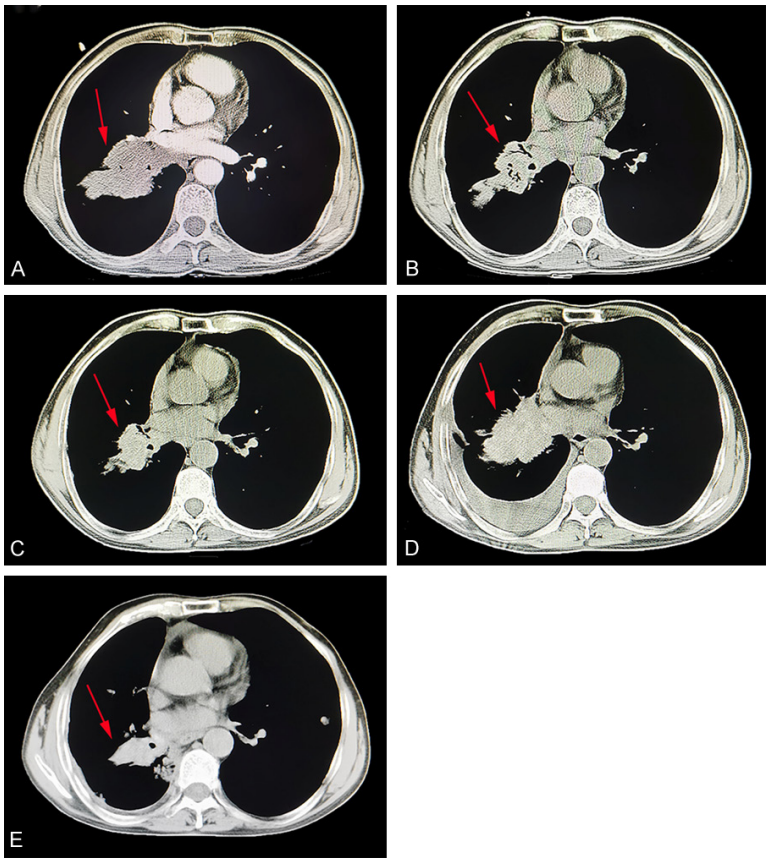

Figure 4. Chest CT at different times of treatment in a typical case of lung squamous cell carcinoma patient. A. A 96 mm * 58 mm tumor in the right hilum of the lung grew across the oblique fissure toward the lower lobe. B. After treatment with docetaxel plus cisplatin for 2 months, the tumor in the right hilum was significantly reduced, with a size of 63 mm * 38 mm. C. Maintaining the original chemotherapy regimen for 2 month, the Hilum tumor shrank again. D. The patient was admitted to hospital again after discharge. Chest CT showed that the tumor was enlarged with a small amount of pleural effusion. E. After radiotherapy combined with thoracic perfusion chemotherapy, the tumor shrank again and pleural effusion reduced.

Disclosure of conflict of interest

None.

Address correspondence to: Jianhong Zuo, School of Medicine, University of South China, 28 Changsheng Road, Hengyang 421001, Hunan, P. R. China. E-mail: 632138414@qq.com

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