

# Associations of lymphocyte percentage and red blood cell distribution width with risk of lung cancer

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## Abstract

**Objective:** There is ample evidence to indicate that inflammation is involved in tumorigenesis. Lymphocyte percentage (LYM%) and red blood cell distribution width (RDW) are easily measured indicators of systemic inflammation. This study aimed to investigate the associations between LYM% and RDW and the risk of lung cancer.

**Methods:** We retrospectively reviewed the records of 430 patients with lung cancer and 158 healthy individuals (control group). Twenty clinical characteristics were analyzed, including LYM% and RDW. Significant laboratory indices were determined by univariate analysis and logistic regression was conducted to identify independent predictors of lung cancer risk.

**Results:** Patients with lung cancer had significantly lower LYM% and higher RDW levels compared with healthy controls. LYM% and RDW were confirmed to be independent predictors of lung cancer risk. LYM% also differed significantly among different histological subtypes of lung cancer.

**Conclusion:** A high risk of lung cancer was closely correlated with low LYM% and high RDW. LYM% and RDW are easily measured and may therefore aid the assessment and timely screening of lung cancer risk.

## Keywords

Lymphocyte percentage, red blood cell distribution width, lung cancer risk, inflammation, lung cancer subtype, cancer screening

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## Introduction

Lung cancer is one of the most serious public health problems worldwide in terms of its incidence and mortality.<sup>1</sup> Lung cancer accounts for around 36% and 29%, respectively, of the average annual cancer-related morbidity and mortality in China.<sup>2</sup> However, despite recent advances in the treatment of lung cancer, including molecular-targeted therapy, the early diagnosis of lung cancer remains barely satisfactory. Most patients are diagnosed at an advanced stage, and the 5-year overall survival rate is <18%,<sup>3</sup> while the low sensitivity of traditional tumor markers in patients with early lung cancer often leads to a delayed diagnosis.<sup>4</sup> New biomarkers to allow the timely and accurate screening and diagnosis of lung cancer would therefore be of great clinical value.

There is increasing evidence to indicate that inflammation and a weak immune system participate in the growth, progression, and metastasis of cancers, including lung cancer. Biological, chemical, and physical factors that contribute to inflammation increase the risk of cancer by promoting angiogenesis, aggravating DNA damage, and facilitating invasion.<sup>5-7</sup> We accordingly speculated that the risk of lung cancer may be assessed by examining changes in indicators of inflammation, which may in turn aid its early diagnosis.

Lymphocytes have anti-inflammatory properties and to play an important role in anti-tumor immunity. An elevated lymphocyte level is routinely used as an indicator of inflammation.<sup>8</sup> Overall changes in lymphocytes with regard to inflammation and the immune state may be expressed as the lymphocyte percentage (LYM%) (i.e., the ratio of lymphocytes to leukocytes), which is considered to be a more accurate measure than lymphocyte count alone. Previous studies reported that lymphocytes were associated with postoperative cancer

survival,<sup>9</sup> chemotherapy efficacy,<sup>10</sup> and the prognosis of palliative care.<sup>11</sup> However, the association between lymphocytes, particularly the LYM%, and cancer risk has not been determined.

Red cell distribution width (RDW) is a measure of erythrocyte volume variability,<sup>12</sup> and has also recently has been considered as an indicator of inflammation. Elevated RDW was shown to contribute to cancer progression and prognosis in relation to breast,<sup>13</sup> lung,<sup>14</sup> esophageal,<sup>15</sup> and gastrointestinal tract cancers.<sup>16</sup> In addition to being a routine marker of erythrocyte heterogeneity, RDW is also used for the differential diagnosis of anemia.<sup>17</sup> Nevertheless, the direct association between RDW and cancer risk remains unclear.

We conducted a preliminary retrospective study to investigate the associations between LYM% and RDW and the risk of lung cancer, to determine the feasibility of applying these inflammation markers for the timely screening for lung cancer.

## Methods

This study was approved by the Ethics Committee and Institutional Review Board of the First Affiliated Hospital of Nanchang University and was carried out in accordance with national law and the current revised Declaration of Helsinki. Informed consent was obtained from all participants in the study.

### *Study population*

The initial study population included 546 consecutive patients with lung cancer treated at the Department of Cardiothoracic Surgery at the First Affiliated Hospital of Nanchang University (Jiangxi, China) from May 2016 to August 2018. The inclusion criteria were patients aged  $\geq 18$  years with histopathologically corroborated lung cancer (stage I–IV) and complete clinical and

laboratory data, with no treatment before serum collection. Patients were excluded if they had any clinical evidence of serious infection, hematological diseases, or other inflammatory conditions, tumors other than lung cancer of any origin, or if they had received a blood transfusion within 4 months before admission.

Patients who met the above criteria were divided into four groups according to the following histopathological cancer subtypes: lung squamous cell carcinoma; lung adenocarcinoma; large cell lung cancer; and small cell lung cancer. All histological diagnoses were determined according to the classification criteria of the World Health Organization and the International Association for Lung Cancer Research. Lung cancer stage was confirmed according to the tumor-node-metastasis staging system of the American Joint Committee on Cancer/Union for International Cancer Control (Eighth Edition, 2017).

An additional age- and sex-matched control group of healthy individuals was selected from the Physical Examination Center of the First Affiliated Hospital of Nanchang University between August 2017 and August 2018. None of the control subjects had a history of lung cancer or other diseases that might affect LYM% or RDW.

### *Clinical parameters and laboratory results*

Clinicopathological and laboratory data for the patients were obtained from an electronic database of medical records. The clinicopathological variables included age, sex, histological cancer subtype, and tumor stage. The laboratory variables consisted of routine blood examination, liver function tests, and tumor markers.

Routine blood examinations were conducted using an automated hematology analyzer XE-5000 (Sysmex, Kobe, Japan). The measured parameters included white and red blood cell counts (WBC and

RBC, respectively), hemoglobin, mean cell volume, RDW, absolute lymphocyte count (LYM), LYM%, absolute monocyte count (MON), and monocyte percentage (MON%). The normal levels of LYM% and RDW were considered as 20%–50% and 11.5%–14.5%, respectively.

Liver function tests (alanine aminotransferase, aspartate aminotransferase, total protein, and albumin) were detected using an automatic biochemical analyzer 7600 (Hitachi High-tech, Tokyo, Japan).

Tumor markers were analyzed using a Roche E601 analyzer (Roche, Basel, Switzerland) and included  $\alpha$ -fetoprotein, carcinoembryonic antigen (CEA), and carbohydrate antigens CA12-5, CA15-3, and CA19-9.

### *Statistical analyses*

All statistical analyses were performed using IBM SPSS statistical software 23.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 7.00 (GraphPad, La Jolla, CA, USA). The normality of continuous variables was examined with the Kolmogorov–Smirnov test. Continuous variables with a normal distribution are expressed as mean  $\pm$  standard deviation and were compared by one-way analysis of variance. Skewed continuous variables are presented as median/interquartile range and were assessed by the Kruskal–Wallis H test. Categorical variables are shown as percentages and were analyzed by  $\chi^2$  tests. Associations between continuous variables were evaluated using Spearman's correlation analysis. Logistic regression analysis was applied to determine associations between laboratory indicators and lung cancer risk. All tests were two-sided and the significance level was set at  $P < 0.05$ .

## Results

### Clinical characteristics

A total of 430 patients with histopathologically corroborated lung cancer (stage I–IV) and 158 healthy controls were finally included in this study. The clinical characteristics of all the subjects are summarized in Table 1. The median LYM% was significantly lower in the lung cancer patients (9.5/13.5–24.7) compared with the healthy controls (35.4/30.9–40.3) ( $P < 0.001$ ) (Figure 1a), while the RDW was significantly higher in patients with lung cancer (15.10/13.80–16.80) than in the controls (13.1/12.7–13.5) ( $P < 0.001$ ) (Figure 1b).

Albumin, RBC count, hemoglobin, and LYM were all significantly lower in the

patients compared with the controls (all  $P < 0.05$ ), while WBC, MON, CEA, CA12-5, CA15-3, and CA19-9 were all significantly higher in patients with lung cancer (all  $P < 0.001$ ). The patient and control groups were statistically comparable with regard to age, sex, alanine aminotransferase, aspartate aminotransferase, total protein, mean cell volume, MON%, and  $\alpha$ -fetoprotein.

### Associations among LYM%, RDW, and other biomarkers in lung cancer patients

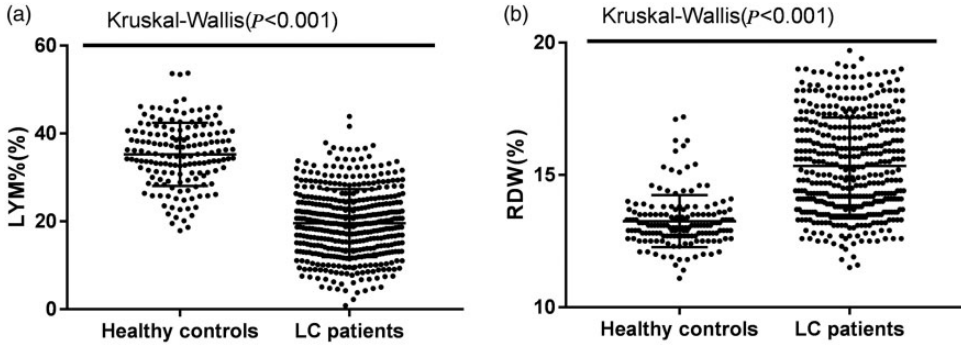
The data were evaluated using Spearman's correlation test (Table 2). RDW was significantly and positively correlated with LYM ( $\rho = 0.119$ ); LYM% was significantly and positively correlated with albumin

**Table 1.** Clinical characteristics of subjects.

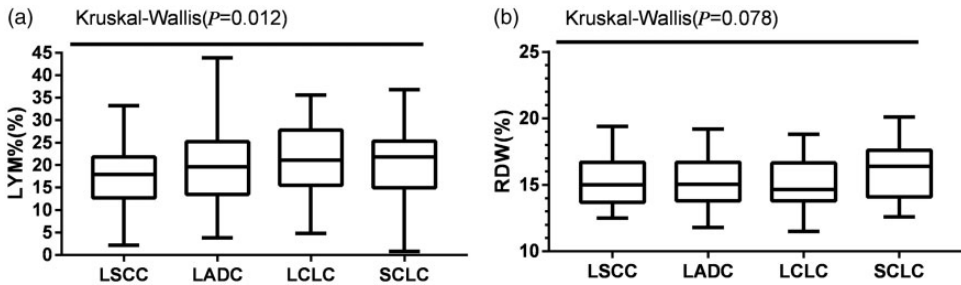
Variable	Patients	Healthy controls	P value
Age (years)	62 (26–87)	60 (45–73)	0.071
Sex (male/female)	295/135	99/59	0.198
ALT (U/L)	18 (12–26)	19 (14–26)	0.118
AST (U/L)	22 (18–27)	22 (17–28)	0.702
TP (g/L)	68.0 (63.2–72.1)	67.6 (63.8–70.2)	0.293
ALB (g/L)	39.7 (35.6–43.2)	41.0 (39.1–42.7)	0.002
WBC ( $10^9/L$ )	6.75 (5.17–8.41)	5.99 (5.03–6.74)	<0.001
RBC ( $10^9/L$ )	4.26 (0.60)	4.70 (0.58)	<0.001
Hb (g/L)	126 (115–138)	147 (135–157)	<0.001
MCV (fL)	90.4 (87.2–93.7)	90.8 (88.3–93.3)	0.374
RDW (%)	15.10 (13.80–16.80)	13.1 (12.7–13.5)	<0.001
LYM ( $10^9/L$ )	1.43 (1.10–1.77)	2.10 (1.75–2.63)	<0.001
LYM% (%)	19.5 (13.5–24.7)	35.4 (30.9–40.3)	<0.001
MON ( $10^9/L$ )	0.47 (0.32–0.65)	0.41 (0.32–0.52)	0.014
MON% (%)	6.7 (5.5–8.6)	6.9 (5.6–8.4)	0.428
AFP (ng/mL)	2.59 (1.78–3.67)	2.78 (1.88–3.54)	0.634
CEA (ng/mL)	6.33 (3.10–17.73)	1.56 (0.96–2.18)	<0.001
CA12-5 (U/mL)	30.26 (17.85–73.97)	9.83 (7.19–13.05)	<0.001
CA15-3 (U/mL)	14.58 (8.80–24.14)	8.02 (4.31–11.31)	<0.001
CA19-9 (U/mL)	15.11 (9.35–29.13)	8.80 (6.18–12.60)	<0.001

Values given as median (interquartile range).

ALT: alanine aminotransferase, AST: aspartate aminotransferase, TP: total protein, ALB: albumin, WBC: white blood cell count, RBC: red blood cell count, Hb: hemoglobin, MCV: mean cell volume, RDW: red blood cell distribution width, LYM, absolute lymphocyte count, LYM%: lymphocyte percentage, MON: absolute monocyte count, MON%: monocyte percentage, AFP:  $\alpha$ -fetoprotein, CEA: carcinoembryonic antigen, CA: cancer antigen. Data analyzed by Kolmogorov–Smirnov test.  $P < 0.05$  was considered significant.



**Figure 1.** (a) Median LYM% in lung cancer patients and healthy controls. (b) Median RDW in lung cancer patients and healthy controls. LYM%: lymphocyte percentage, RDW: red blood cell distribution width, LC: lung cancer.



**Figure 2.** (a) LYM% as median in different lung cancer subtypes. (b) RDW as median in different lung cancer subtypes.

( $\rho = 0.281$ ), RBC count ( $\rho = 0.139$ ), hemoglobin ( $\rho = 0.147$ ), and LYM ( $\rho = 0.401$ ); and LYM% was significantly and negatively correlated with WBC ( $\rho = -0.426$ ) and MON ( $\rho = -0.312$ ) (both  $P < 0.001$ ). Neither RDW nor LYM% was significantly correlated with any of the tested common lung cancer tumor markers (i.e., CEA, CA12-5, CA15-3, and CA19-9).

**Logistic regression analysis of predictors of lung cancer risk**

The results of the logistic regression analysis are shown in Table 3. Univariate analysis indicated that albumin, WBC and RBC counts, hemoglobin, LYM, LYM%, MON,

CEA, CA12-5, CA15-3, and CA19-9 differed significantly between the patients and healthy controls. These indicators were then entered into the multivariate logistic regression analysis, which identified only RDW (odds ratio (OR) 2.757, 95% confidence interval (CI): 1.694–4.485,  $P < 0.001$ ), LYM% (OR 0.759, 95% CI: 0.652–0.861,  $P < 0.001$ ), and MON (OR 0.015, 95% CI: 0.000–0.642,  $P = 0.028$ ) as independent predictors of lung cancer risk.

**Associations among LYM%, RDW, and lung cancer subtypes**

The associations among LYM%, RDW, and lung cancer subtypes are shown in

**Table 2.** Correlations between LYM%, RDW and other biomarkers in lung cancer patients.

Analyte	RDW		LYM%	
	Spearman's $\rho$	P value	Spearman's $\rho$	P value
ALB	0.09	0.062	0.281	<0.001
WBC	-0.051	0.289	-0.426	<0.001
RBC	-0.018	0.705	0.139	0.004
Hb	-0.023	0.634	0.147	0.002
RDW	1	N/A	0.044	0.367
LYM	0.119	0.014	0.401	<0.001
LYM%	0.044	0.367	1	N/A
MON	-0.003	0.957	-0.312	<0.001
CEA	0.009	0.854	-0.047	0.331
CA12-5	-0.047	0.332	-0.02	0.678
CA15-3	-0.018	0.709	-0.008	0.87
CA19-9	-0.077	0.111	-0.02	0.677

ALB: albumin, WBC: white blood cell count, RBC: red blood cell count, Hb: hemoglobin, RDW: red blood cell distribution width, LYM, absolute lymphocyte count, LYM%: lymphocyte percentage, MON: absolute monocyte count, CEA: carcinoembryonic antigen, CA: cancer antigen, N/A: not analyzed. Spearman's correlation test was used to analyze data.  $P < 0.05$  was considered significant.

Table 4. LYM% and RDW showed skewed distributions among the different subtypes and were assessed using the Kruskal–Wallis H test. LYM% differed significantly among the lung cancer subtypes, with the highest median LYM% in patients with small cell lung cancer (21.80/14.95–25.35), followed by large cell lung cancer (21.10/15.53–27.78), lung adenocarcinoma (19.65/13.48–25.23), and lung squamous cell carcinoma (17.90/12.70–21.80) (Figure 2a). There were no significant relationships between RDW and lung cancer subtypes (Kruskal–Wallis H test) (Figure 2b).

## Discussion

This retrospective study investigated associations between LYM% and RDW as routine markers of inflammation and the risk of lung cancer. Patients with lung cancer and healthy individuals were compared in terms of 20 laboratory variables, including LYM% and RDW. LYM% was significantly lower in

the patients compared with the control group, while RDW was significantly higher. In addition, Spearman's correlation analysis showed a positive association between RDW and LYM, but no correlation between LYM% or RDW and any of the traditional tumor markers.

Spearman's correlation analysis also revealed that LYM% was significantly and negatively correlated with MON, consistent with the results of Chen et al.<sup>9</sup> in lung cancer. Previous studies showed that some monocytes can differentiate into M1 or M2 macrophages. M1 macrophages produce reactive oxygen species and nitrogen intermediates that result in DNA damage in proliferative cells and support the occurrence of cancer, while M2 macrophages promote angiogenesis, tissue remodeling and repair, and are generally associated with tumor progression. Both M1 and M2 macrophages can inhibit anti-tumor immune responses and promote a reduction in lymphocytes.<sup>9,18–20</sup> This may explain the negative correlation



**Table 3.** Logistic regression analysis to determine predictors of lung cancer risk.

Variable	Univariate			Multivariate		
	OR	95%CI	P value	OR	95%CI	P value
Age	1.019	0.999–1.039	0.066			
Sex	1.302	0.889–1.907	0.175			
ALT	0.996	0.977–1.015	0.648			
AST	1.012	0.985–1.040	0.374			
TP	1.005	0.976–1.035	0.729			
ALB	0.927	0.891–0.965	<0.001	0.964	0.822–1.131	0.656
WBC	1.214	1.114–1.323	<0.001	1.518	0.940–2.449	0.088
RBC	0.283	0.200–0.402	<0.001	0.378	0.105–1.356	0.135
Hb	0.934	0.921–0.947	<0.001	0.984	0.934–1.037	0.551
MCV	0.989	0.959–1.020	0.478			
RDW	2.979	2.386–3.720	<0.001	2.757	1.694–4.485	<0.001
LYM	0.116	0.077–0.176	<0.001	0.443	0.119–1.655	0.226
LYM%	0.769	0.736–0.803	<0.001	0.749	0.652–0.861	<0.001
MON	2.905	1.329–6.350	0.008	0.015	0.000–0.642	0.028
MON%	0.998	0.961–1.035	0.897			
AFP	1.055	0.962–1.158	0.255			
CEA	2.470	2.025–3.011	<0.001	2.624	1.554–4.430	<0.001
CA12-5	1.167	1.129–1.207	<0.001	1.150	1.069–1.237	<0.001
CA15-3	1.158	1.117–1.202	<0.001	1.106	0.984–1.243	0.090
CA19-9	1.096	1.065–1.128	<0.001	1.038	0.958–1.124	0.365

OR: odds ratio, CI: confidence interval, ALT: alanine aminotransferase, AST: aspartate aminotransferase, TP: total protein, ALB: albumin, WBC: white blood cell count, RBC: red blood cell count, Hb: hemoglobin, MCV: mean cell volume, RDW: red blood cell distribution, LYM, absolute lymphocyte count, LYM%: lymphocyte percentage, MON: absolute monocyte count, MON%: monocyte percentage, AFP:  $\alpha$ -fetoprotein, CEA: carcinoembryonic antigen, CA: cancer antigen.  $P < 0.05$  was considered significant.

**Table 4.** Relationships between LYM% and RDW and lung cancer subtype.

Group	n (%)	LYM%	RDW
Lung cancer	430	19.50 (13.48–24.65)	15.10 (13.80–16.80)
Lung squamous cell carcinoma	115 (26.7)	17.90 (12.70–21.80)	15.00 (13.70–16.70)
Lung adenocarcinoma	226 (52.6)	19.65 (13.48–25.23)	15.05 (13.80–16.70)
Large cell lung cancer	52 (12.1)	21.10 (15.53–27.78)	14.65 (13.80–16.65)
Small cell lung cancer	37 (8.6)	21.80 (14.95–25.35)	16.40 (14.10–17.60)
P value		0.012	0.078

Values given as median (interquartile range).

LYM%: lymphocyte percentage, RDW: red cell distribution width. Values are shown as median and interquartile range. Data were analyzed by the Kruskal–Wallis H test.  $P < 0.05$  was considered significant.

between monocytes and LYM% in patients in the present study.

The current logistic regression analysis identified LYM% and RDW as independent

predictors of lung cancer risk. However, the precise mechanism linking RDW, LYM%, and lung cancer remains unclear. Cancer is widely supposed to be the result

of chronic inflammation.<sup>21</sup> Inflammation is involved in all stages of tumorigenesis, leading to invasion and metastasis by providing important molecules to the tumor microenvironment.<sup>5,22</sup> These molecules include growth factors that maintain signals for proliferation, survival factors that limit apoptosis, angiogenic factors, and extracellular matrix-modifying enzymes that are linked to angiogenesis, invasion, and metastasis. Moreover, inflammatory cells can release chemicals such as reactive oxygen species, which are associated with positive mutagenicity and further promote the development of malignant tumors. There is also extensive epidemiological evidence for the existence of chronic inflammation in the etiology of lung cancer.<sup>6,7,23–25</sup>

Inflammation causes an increase in RDW. Inflammation may cause impaired iron metabolism and inhibit the erythropoietin response, resulting in entry of a large number of immature erythrocytes into the peripheral blood circulation from the bone marrow. The subsequent increased ratio of ineffective hematopoiesis and volume heterogeneity of peripheral blood erythrocytes ultimately causes changes in erythrocyte maturation.<sup>26–28</sup>

Because tumorigenesis, including lung cancer, is closely related to inflammation, high RDW levels, may reflect the severity of inflammation and thus increased risk of lung cancer, which may explain the positive correlation between RDW and lung cancer risk observed in the present study.

Leukocytes include lymphocytes, neutrophils, eosinophils, basophils, and monocytes, and LYM%, as the lymphocyte-to-leukocyte ratio, provides a marker of the anti-inflammatory response and immune status. Iseki et al.<sup>29</sup> considered that LYM% was also affected by neutrophils and monocytes, which may explain why LYM% reflects systemic inflammation more accurately than the peripheral blood lymphocyte count. Anti-inflammatory

surveillance, as a function of lymphocytes, inhibits tumor cell proliferation. About 80% of lymphocytes are T cells, including cytotoxic CD8+ T cells, which inhibit tumor growth and destroy tumor cells by modifying the tumor stroma and epithelium. In addition, T helper cells (Th cells), also known as CD4+ T cells, help B cells mature into plasma cells and memory B cells and activate CD8+ T cells to play an anti-tumor role.<sup>24,29–31</sup> Thus a low LYM% suggests that the decrease in lymphocytes hinders the immune response and increases the risk of cancers, including lung cancer. This may explain the negative correlation between LYM% and the risk of lung cancer in the present study.

The current study showed a significant difference in LYM% among patients with different histological subtypes of lung cancer. Small cell lung cancer was associated with the highest LYM%, followed by large cell lung cancer, lung adenocarcinoma, and lung squamous cell carcinoma. However, the mechanism responsible for the relationship between LYM% and histopathological differentiation of lung cancer remains unclear, and LYM% cannot currently serve as a biomarker to differentiate among lung cancer subtypes.

This study was limited by its retrospective design, and was therefore vulnerable to bias in terms of data selection and analysis. In addition, the sample size was relatively small, especially in terms of patients with small cell and large cell lung cancer subtypes. Further large-scale prospective studies are therefore needed to verify the associations between LYM%, RDW, and lung cancer risk.

In conclusion, LYM% and RDW are routine inflammatory clinical markers that can be measured economically, quickly, and easily. These markers of chronic inflammation showed strong associations with lung cancer risk, suggesting that LYM% and RDW may be independent predictors of



lung cancer risk, with great clinical value for the timely screening of patients.

### Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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