



Combination of albumin concentration and neutrophil-to-lymphocyte ratio for predicting overall survival of patients with non-small cell lung cancer

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Background: Lung cancer contributes significantly to the total of cancer-linked deaths globally, accounting for 1.3 million deaths each year. Preoperative albumin (Alb) concentration and neutrophil-to-lymphocyte ratio (NLR) may reflect chronic inflammation and be used to predict lung cancer outcomes.

Methods: The clinical records of 293 patients with non-small cell lung cancer (NSCLC) in Fujian Medical University Cancer Hospital & Fujian Cancer Hospital were reviewed retrospectively in this current study. Clinicopathologic pretreatment, including NLR, Glasgow prognostic score (GPS), and post-treatment value, such as tumor-node-metastasis (TNM) were documented. The cut-off finder application was employed to calculate the optimal threshold values. The significance of Alb concentration combined with NLR (COA-NLR) on the prediction of overall survival (OS) was explored using Kaplan-Meier analysis along with Cox proportional hazards.

Results: The results revealed that COA-NLR could independently assess the OS of patients with NSCLC [hazard ratio (HR) =1.952, 95% confidence interval (CI): 1.367 to 2.647, P<0.001]. Moreover, the 3-year OS rates were 87.2%, 68.5%, and 52.8% for the COA-NLR =0, COA-NLR =1, and COA-NLR =2, respectively (P<0.001).

Conclusions: Preoperative COA-NLR value can effectively stratifies prognosis in NSCLC patients by classified patients into three independent groups. It can be adopted as an effective biomarker for prognosis in NSCLC patients treated with resection.

Keywords: Albumin (Alb); prognosis; neutrophil-to-lymphocyte ratio (NLR); non-small cell lung cancer (NSCLC)

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Introduction

Lung cancer contributes significantly to the total number of cancer-linked deaths globally, is responsible for

1.3 million deaths each year (1), and the most common cancer diagnosed in men in China. Among lung cancers, non-small-cell lung cancer (NSCLC) constitutes 85%

of all primary lung cancers (2). Although remarkable advancements have been made in the treatment as well as clinical diagnosis of NSCLC, the median survival of this cancer remains unsatisfactory.

Predicting the outcomes in individual patients is difficult. Previously, the tumor-node-metastasis (TNM) system, genetic biomarkers, along with histological subtype served as the common predictive tools for estimating overall survival (OS) (3). Nevertheless, patients in the TNM stage or with the histopathological subtype exhibited remarkably diverse survival, and due to the high cost of genetic biomarkers, their clinical use was limited.

The systemic inflammatory response (SIR) plays an important role in the lung cancer prognosis. The biomarkers include C-reactive protein (CRP), albumin (Alb), neutrophil-to-lymphocyte ratio (NLR) and fibrinogen (Fib), which have been commonly observed in lung cancer patients. Of these, low Alb concentration are associated with poor survival, and preoperative serum Alb concentration can accurately predicted long-term outcomes in patients with cancer. Meanwhile, NLR has been candidate signatures to reveal the status of chronic inflammation and estimate the outcome in lung cancer patients (4-6) Therefore, we hypothesized that the combination of Alb and NLR would be better predict the prognosis in NSCLC. In this paper, we developed a new inflammation-based prognostic system, referred to as the combination of Alb concentration and NLR (COA-NLR), which may better reflect systemic inflammation level and stratify the patients into different risk categories.

Herein, we verified the prognostic significance of Alb and NLR in individuals with NSCLC treated with lung resection. Moreover, we also evaluated the relationship of COA-NLR groups with the clinic-pathologic features or the clinical laboratory variables.

We present the following article in accordance with the REMARK reporting checklist (available at <https://dx.doi.org/10.21037/jtd-21-1320>).

Methods

Eligible patients

This retrospective study examined data of NSCLC patients who had undergone pulmonary resection (pneumonectomy or lobectomy) and dissection of the hilar, as well as mediastinal lymph nodes at the Fujian Provincial Tumor Hospital, China, between January 2006 and January 2017. All NSCLC patients were newly diagnosed, then classified

via clinical symptoms along with pathological grading, per the international association guidelines for lung cancer TNM staging (7th edition of the TNM classification). All participants had undergone surgical resection, and some had been given adjuvant radiotherapy or chemotherapy when needed. Patients with hematological disease, autoimmune disease, and infection were excluded. On the basis of the inclusion and exclusion criteria above, a total of 293 NSCLC patients were analyzed. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Fujian Medical University Cancer Hospital & Fujian Cancer Hospital, China, and the need for informed consent was waived given the use of retrospective data.

We collected clinic-pathologic findings of the 293 participants, including age, Glasgow prognostic score (GPS), TNM stage, and blood cell count. Within 1 week before surgery, we collected peripheral venous blood from each participant between 8 am and 10 am. The 7th edition of the TNM classification was employed to assign tumor stages (7).

Definition of COA-NLR

Through dividing the neutrophil numbers by the absolute lymphocyte numbers, the NLR was determined. The receiver operating characteristic (ROC) curves were adopted to explore the threshold values of the pre-operative NLR, as well as Alb. The recommended NLR threshold value was determined on the basis of the predominant point on the ROC curve for sensitivity (0.429) and specificity (0.700), respectively. The two parameters yielded a threshold value of 2.565; therefore, we defined the recommended threshold value of NLR as 2.5. The area under the ROC curve (AUC) was 0.672. Besides, the recommended preoperative Alb threshold value was defined as 35 g/L, since the dominant point on the ROC curve yielded a threshold value of 35.7 g/L for sensitivity (0.514), as well as specificity (0.785). The AUC was 0.644.

The COA-NLR was computed based on data obtained on the day of admission as shown: patients exhibiting an elevated NLR (>2.5) and reduced Alb value (<35 g/L) were designated a score of 2, and patients exhibiting either, or neither, were designated a score of 1 or 0, respectively.

Follow up

A regular follow-up examination was conducted once every

6 months to determine the survival data via retrieval of medical records, email, as well as telephone, with 31 January 2017 being the deadline of the follow-up. We defined OS time as the time from the first treatment to death or last follow-up.

Statistical analysis

All recorded data are presented as mean \pm standard deviation (SD). The chi-squared test along with the Kruskal-Wallis test were adopted to determine the differences among groups.

To determine the optimal cutoff values of each clinical laboratory variable, a ROC curve was created, and the cutoff values were set as the point on the curve that was closest to the upper left-hand corner of the plot.

The OS rates were determined using the Kaplan-Meier approach, and comparisons were determined by log-rank test. Each variable was assessed on the univariate analysis, and then calculated on the multivariable Cox proportional hazards model to validate their independent prognostic value. Statistical analyses were performed using the software SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). A *P* value <0.05 indicated statistical significance.

Results

Patients characteristics

Overall, 293 consecutive patients with complete medical data and follow-up data were enrolled. The distribution of the clinical background features of the three groups of participants were divided according to the COA-NLR, as shown in *Table 1*. The results did not reveal any remarkable differences among the groups, except for gender, tobacco, GPS, tumor status, and TNM status.

Prognostic analysis

Table 2 demonstrates that OS, CRP, white blood cell (WBC), neutrophil, lymphocyte, NLR, hemoglobin (Hb), platelet (PLT), Alb, glucose, and lactate dehydrogenase (LDH) were significantly associated with the three groups of NSCLC patients.

During the observation period, 70 (23.9%) participants died. Univariate analysis along with multivariate Cox proportional hazards model assessments were performed to explore the relationship between clinical characteristics

and OS.

Univariate analysis revealed that adjuvant therapy ($P=0.003$), COA-NLR ($P<0.001$), GPS ($P<0.001$), WBC ($P<0.001$), neutrophil ($P<0.001$), NLR ($P<0.001$), PLT ($P=0.001$), Alb ($P<0.001$), alanine transaminase (ALT) ($P=0.031$), glucose ($P=0.019$), lymph status ($P<0.001$), tumor status ($P=0.001$), metastasis ($P=0.004$) and TNM status ($P<0.001$) were significantly associated with OS in patients with NSCLC. Age, gender, body mass index (BMI), smoking, CRP, Hb, and LDH did not estimate OS following the surgery (*Table 3*).

Multivariate assessments showed that COA-NLR [hazard ratio (HR) = 1.952, 95% confidence interval (CI): 1.367 to 2.647, $P<0.001$], lymph (HR = 0.486, 95% CI: 0.260 to 0.985, $P=0.045$), PLT (HR = 1.878, 95% CI: 1.403 to 3.970, $P=0.007$), glucose (HR = 1.450, 95% CI: 1.125 to 3.443, $P=0.018$), and TNM status (HR = 1.852, 95% CI: 1.523 to 2.547, $P<0.001$) were independent predictive factors (*Table 4*).

The Kaplan-Meier approach was employed to create OS curves, as stratified on the basis of the COA-NLR score and TNM status. The 3-year OS rates were 87.2%, 68.5%, and 52.8% for the COA-NLR = 0, COA-NLR = 1, and COA-NLR = 2, respectively. The log-rank test was used to explore the differences in survival, which exhibited remarkable distinctions for all strata ($P<0.001$, *Figure 1*).

Discussion

Herein, we found that patients with COA-NLR 1 or 2 have lower GPS, higher T stage, and higher TNM stage in contrast with those with COA-NLR 0 (*Table 1*). Similarly, NSCLC patients with lower GPS, higher T stage, and higher TNM stage had poor OS (*Table 3*). As COA-NLR constitutes systemic inflammatory response syndrome (SIRS)-linked characteristics—NLR and Alb level, it may well reflect the severity of the disease, so it was reasonable to find significant differences between COA-NLR groups regarding GPS, T stage, and TNM stage. Therefore, as predicted, we found that there were also significant differences between OS of NSCLC patients and traditional severity indexes, such as GPS, T stage, and TNM stage in NSCLC patients.

Furthermore, we also established that COA-NLR was an independent predictive factor, COA-NLR with a lower score was linked to better OS in individuals with NSCLC. The NLR is an index of circulating immune cells; the new predictor, COA-NLR, may better reveal the balance of systemic inflammation with host immune response for the

Table 1 Relationships of clinical characteristics with the COA-NLR in individuals with NSCLC

Variables	COA-NLR 0 (n=149)	COA-NLR 1 (n=108)	COA-NLR 2 (n=36)	P value
Age, years				
>65	31	34	12	0.094
<65	118	74	24	
Gender				
Male	82	88	34	<0.001
Female	67	20	2	
Adjuvant therapy				
None	32	23	8	0.993
Chemo-radiotherapy	117	85	28	
Tobacco				
Yes	51	62	20	<0.001
No	98	46	16	
GPS				
0	94	39	0	<0.001
1	55	63	12	
2	0	6	24	
Pathologic N stage				
N0	110	74	24	0.541
N1–N3	39	34	12	
Pathologic T stage				
T1–T2	77	27	3	<0.001
T3–T4	72	81	33	
Metastasis				
No	141	103	35	0.784
Yes	8	5	1	
TNM status				
I	81	42	9	0.013
II	28	35	13	
III	32	13	13	
IV	8	76	1	

COA-NLR, combination of albumin concentration and neutrophil-to-lymphocyte ratio; NSCLC, non-small cell lung cancer; GPS, Glasgow prognostic score; TNM, tumor-node-metastasis.

progress of cancer. What's more, COA-NLR could be a sign that stands for immunity status. As inflammatory response can suppress antitumor immunity and hypoalbuminemia

can impair cellular immunity. Lower score of COA-NLR means better immunity status, which was better for the outcomes of lung cancer.

Table 2 Relationships of clinical laboratory features with the COA-NLR in individuals with NSCLC

Variables	COA-NLR 0 (n=149)	COA-NLR 1 (n=108)	COA-NLR 2 (n=36)	P value
Age, years	57±9	60±9	61±10	0.063
BMI, kg/m ²	23±2.9	23±3.3	22±3.1	0.077
OS (months)	59±22	49±26	36±27	<0.001
CRP, mg/dL	1.1±1.2	1.7±1.9	2.6±1.6	0.001
WBC, 10 ⁹ /L	6.9±1.7	8.5±2.2	10.0±2.6	<0.001
Neutrophil, 10 ⁹ /L	3.8±1.2	5.7±2.2	7.0±2.0	<0.001
Lymph, 10 ⁹ /L	2.3±0.6	1.8±0.5	1.9±0.6	<0.001
NLR	1.7±0.5	3.5±2.9	4.0±1.6	<0.001
Hb, g/L	137±14	135±15	125±14	<0.001
PLT, 10 ⁹ /L	242±70	257±76	342±121	<0.001
Alb, g/L	40±2.6	37±3.9	32±2.4	<0.001
Glucose, mmol/L	5.5±1.0	5.6±1.5	5.2±1.3	0.023
LDH, U/L	147±24	181±110	139±25	0.044
ALT, U/L	20.9±15.9	20.9±13.6	29.6±30.4	0.311

COA-NLR, combination of albumin concentration and neutrophil-to-lymphocyte ratio; NSCLC, non-small cell lung cancer; BMI, body mass index; OS, overall survival; CRP, C-reactive protein; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; Hb, hemoglobin; PLT, platelet; Alb, albumin; LDH, lactate dehydrogenase; ALT, alanine transaminase.

Low Alb is common in patients with cancer, as a negative acute-phase protein, it usually integrates with other biomarkers to create novel prognostic signatures, for instance modified GPS (mGPS) (8). Research has documented that the existence of a SIR precedes the development of hypoalbuminemia in cancer patients with poor prognosis (5,9-11). However, the relationship between low Alb and OS have rarely been studied in NSCLC patients. Herein, we found that reduced Alb may be linked to poor OS in individuals with NSCLC ($P<0.001$). The role of NLR in lung cancer was addressed in the previous report (12). High NLR, revealing an elevated inflammatory reaction (dependent on neutrophils) along with a suboptimal lymphocyte-triggered antitumor immune reaction, has been linked to decreased OS in NSCLC (13).

To the best of our knowledge, no studies had previously investigated the relationship of NLR with serum Alb in individuals with NSCLC. Herein, we found that patients with decreased Alb may have shorter OS. Scoring systems that combine NLR and Alb were created, and participants were stratified into three classes. This scoring system was particularly successful in estimating differences among the three study groups in OS in multivariate models. Subgroup

analyses confirmed the validity of this stratification approach. Hence, NLR and serum Alb level were sensitive prognostic markers that provided additional risk stratification for individuals with NSCLC.

Compared with other prognostic biomarkers, such as GPS and TNM status, COA-NLR are more suitable for predicting the outcome in patients with NSCLC. We found that COA-NLR score classified patients into three independent groups, which can more effectively stratify prognosis than TNM status.

Our findings showed complex cross talks of systematic inflammation with the progress of tumors. Both Alb and the NLR may play various roles in systematic inflammation, which lead to the progress of cancer. Serum Alb is mainly synthesized in the liver (14), and reduced pre-operative Alb may indicate a malnourished state (15). Meanwhile, in cancer patients, Alb could reflect sustained systemic inflammation (16-18), low Alb suggests a suppressed immune index. In the immune system, T lymphocytes are pivotal adaptive immune cells, commonly categorized into two subsets on the basis of the expression of CD4 and CD8 receptors (19). Reduced lymphocyte levels can result in immunosuppression, leading to production of inflammatory

Table 3 Univariate Cox proportional hazards model analysis of OS in individuals with NSCLC

Variables	P value	HR	95% CI
Age, years (≥ 65 , < 65)	0.068	1.584	0.967–2.595
Sex (female, male)	0.431	1.236	0.730–2.092
Adjuvant therapy (chemo-radiotherapy, none)	0.003	4.002	1.611–9.940
BMI, kg/m ² (≥ 22.5 , < 22.5)	0.457	1.198	0.744–1.927
Tobacco (no, yes)	0.554	1.152	0.721–1.841
COA-NLR (0, 1, 2)	< 0.001	2.242	1.641–3.063
GPS (0, 1, 2)	< 0.001	1.905	1.351–2.686
CRP, mg/dL (≥ 1 , < 1)	0.141	1.422	0.890–2.272
WBC, 10 ⁹ /L (≥ 6.6 , < 6.6)	< 0.001	3.804	1.889–7.662
Neutrophil, 10 ⁹ /L (≥ 3.7 , < 3.7)	< 0.001	6.091	2.452–15.129
Lymphocyte, 10 ⁹ /L (≥ 2.1 , < 2.1)	0.051	0.620	0.383–1.003
NLR (≥ 2.5 , < 2.5)	< 0.001	2.492	1.548–4.011
Hb, g/L (≥ 145 , < 145)	0.198	0.681	0.379–1.223
PLT, 10 ⁹ /L (≥ 200 , < 200)	0.001	4.570	1.840–11.351
Alb, g/L (≥ 35 , < 35)	< 0.001	2.674	1.651–4.329
ALT, U/L (≥ 20 , < 20)	0.031	1.676	1.049–2.679
LDH, U/L (≥ 138 , < 138)	0.153	1.459	0.869–2.451
Glucose, mmol/L (≥ 6 , < 6)	0.019	1.922	1.112–3.320
Pathologic N stage (N0, N1, N2, N3)	< 0.001	2.518	1.574–4.028
Pathologic T stage (T1, T2, T3, T4)	0.001	2.820	1.544–5.152
Metastasis (no, yes)	0.004	2.960	1.415–6.191
TNM status (I, II, III, IV)	< 0.001	1.953	1.546–2.467

OS, overall survival; NSCLC, non-small cell lung cancer; HR, hazard ratio; CI, confidence interval; BMI, body mass index; COA-NLR, combination of albumin concentration and neutrophil-to-lymphocyte ratio; GPS, Glasgow prognostic score; CRP, C-reactive protein; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; Hb, hemoglobin; PLT, platelet; Alb, albumin; ALT, alanine transaminase; LDH, lactate dehydrogenase; TNM, tumor-node-metastasis.

cytokines in the tumor microenvironment (TME) (20).

Consequently, COA-NLR emerges as a good predictive indicator for individuals with NSCLC. The OS was shorter for high COA-NLR at baseline in contrast with the low COA-NLR at baseline. The COA-NLR escalates the unfavorable impact of Alb, as well as NLR, which elevates the estimated significance for individuals with cancer. Multivariate analyses conducted using the selected parameters in the univariate analyses showed that pre-operative COA-NLR was an independent predictive indicator for individuals with NSCLC with OS. Moreover, data of the Kaplan-Meier test along with log-rank test

illustrated that pre-operative COA-NLR scores could well stratify patients with NSCLC into different risk categories.

This study had numerous limitations. Firstly, this was a single center, retrospective analysis, that enrolled only those patients with complete volumetric measurement, which may have resulted in selection bias. Secondly, the study's sample size was small. There were only 36 participants with high score COA-NLR, a larger amount of data is required to verify these results. Thirdly, although we restricted the impact of some other factors, blood cell counts may have been affected by various factors.

The COA-NLR prospectively emerges as cost-friendly,

Table 4 Multivariate Cox proportional hazards model analysis of OS in individuals with NSCLC

Variables	P value	HR	95% CI
Adjuvant therapy (chemo-radiotherapy, none)	0.129	2.196	0.796–6.085
COA-NLR (0, 1, 2)	<0.001	1.952	1.367–2.647
GPS (0, 1, 2)	0.912	0.961	0.584–1.618
WBC, 10 ⁹ /L (≥6.6, <6.6)	0.131	1.991	0.814–4.859
Neutrophil, 10 ⁹ /L (≥3.7, <3.7)	0.165	2.043	0.726–6.551
Lymph, 10 ⁹ /L (≥2.1, <2.1)	0.045	0.486	0.260–0.985
PLT, 10 ⁹ /L (≥200, <200)	0.007	1.878	1.403–3.970
ALT, U/L (≥20, <20)	0.216	1.362	0.832–2.265
Glucose, mmol/L (≥6, <6)	0.018	1.450	1.125–3.443
Pathologic N stage (N0, N1, N2, N3)	0.088	1.743	0.923–3.213
Pathologic T stage (T1, T2, T3, T4)	0.261	1.574	0.747–2.926
Metastasis (no, yes)	0.267	1.704	0.596–6.470
TNM status (1, 2, 3, 4)	<0.001	1.852	1.523–2.547

OS, overall survival; NSCLC, non-small cell lung cancer; HR, hazard ratio; CI, confidence interval; COA-NLR, combination of albumin concentration and neutrophil-to-lymphocyte ratio; GPS, Glasgow prognostic score; WBC, white blood cell; PLT, platelet; ALT, alanine transaminase; TNM, tumor-node-metastasis.

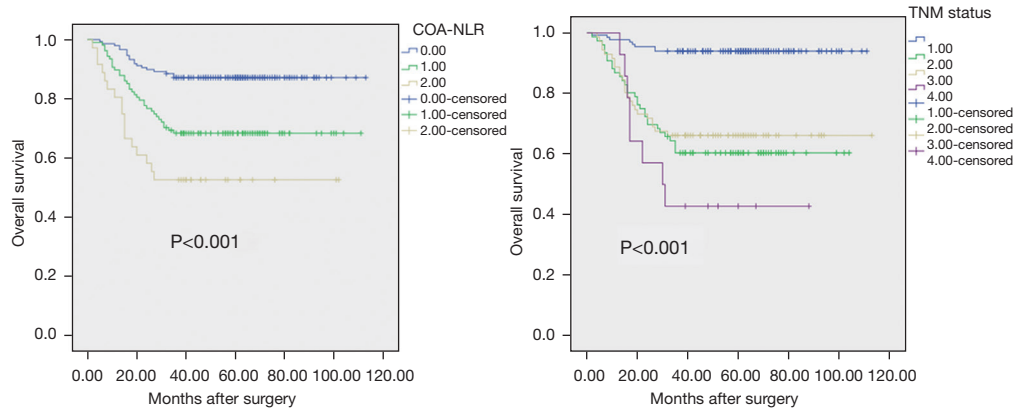


Figure 1 A schematic representation of the Kaplan-Meier graph: OS according to COA-NLR (left) and OS according to TNM status (right) in lung cancer patients undergoing surgery. OS, overall survival; COA-NLR, combination of albumin concentration and neutrophil-to-lymphocyte ratio; TNM, tumor-node-metastasis.

simple, robust, as well as reliable tool accessible to all clinics and easy to adopt into clinical practice. These results could enhance treatment outcomes via informing risk stratification and individual decision-making in recently diagnosed NSCLC patients. Preoperative COA-NLR score can be a useful predictive marker for NSCLC patients with lung resection.

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Footnote

Reporting Checklist: The authors have completed the

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committees of the Fujian Medical University Cancer Hospital & Fujian Cancer Hospital, Fuzhou, China, which waived the requirement for informed consent due to the use of anonymized retrospective data that were routinely collected during the health-screening process.

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