Original Article

Prognostic utility of inflammation-based biomarkers, neutrophil–lymphocyte ratio and change in neutrophil–lymphocyte ratio, in surgically resected lung cancers

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Abstract

BACKGROUND/OBJECTIVE: Given the poor overall survival (OR) and progression-free survival (PFS) rates for lung cancers managed with surgical resection, there is a need to identify the prognostic markers that would improve the risk stratification of patients with operable lung cancer to inform treatment decisions. We investigate the prognostic utility of two established inflammation-based scores, the neutrophil–lymphocyte ratio (NLR) and the change in neutrophil–lymphocyte ratio (ΔNLR), throughout the operative period in a prospective cohort of patients with lung cancer who underwent surgical resection.

METHODS: Demographic, clinical, and treatment details for 345 patients with lung cancer who underwent surgical resection between 2000 and 2019 at multiple centers across Melbourne, Victoria (Australia), were prospectively collected. Preoperative NLR and ΔNLR were calculated after which Cox univariate and multivariate analyses were conducted for OS and PFS against the known prognostic factors.

RESULTS: Both univariate and multivariate analyses showed that preoperative NLR >4.54, as well as day 1 and day 2 postoperative NLR ($P < 0.01$), was associated with increased risk for postoperative mortality (hazard ratio 1.8; $P < 0.01$) and PFS ($P < 0.05$), whereas ΔNLR was not a significant predictor of OS or PFS.

CONCLUSION: Elevated NLR among patients with lung cancer who underwent surgical resection was prognostic for poor OS and PFS, whereas ΔNLR was not found to be prognostic for either OS or PFS. Further research may yet reveal a prognostic value for ΔNLR when compared across a greater time period.

Keywords:

Cancer prognostication, lung cancer, neutrophil–lymphocyte ratio

Lung cancer is the most common cause of cancer death worldwide, with approximately 1.37 million global deaths per year.[1-3] Although surgical resection constitutes an important treatment option for patients with early-stage disease and suitable patients with advanced disease, the recurrence rates have remained high (from 30% to 75%) depending on the final pathological stage,[4] while 5-year survival rates have varied according to the pathological stage, ranging from 70% for Stage IA disease to 40% for Stage IIB.[5] High recurrence rates and associated mortality warrant the investigation of prognostic factors to improve the risk stratification of

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patients with lung cancer who are amenable to surgical resection. Recent research has investigated prognostic pathological biomarkers that may identify patients likely to have poorer overall survival (OS) and progression-free survival (PFS). Prognostic biomarkers that allow for the identification of patients at higher risk for recurrence may be used in the future to determine those who may benefit from adjuvant and neoadjuvant therapies and suitability for surgery.

Prognostication of patients with lung cancer commonly relies on the validated tumor-node-metastasis (TNM) system to guide the clinical decisions, categorized by the American Joint Committee on Cancer (AJCC) stages.[6] Multiple other known tumors and biological factors, such as histological grade, patient age, sex, and performance status, can predispose patients to worse PFS/OS.[7,8] While several novel biomarkers are under investigation for patient prognostication, including plasma exosomal proteins and circulating tumor DNA and RNA,[9-11] testing for such biomarkers is limited by availability and price.

Systemic inflammatory response is intimately linked with cancer and has been implicated in the numerous systemic effects of cancer.[12] The neutrophil–lymphocyte ratio (NLR), a measure that can be extracted from readily available hematological blood tests, has demonstrated prognostic value in a variety of inflammatory conditions and has been explored in both surgical and nonsurgical cancer cohorts.[13] Patients with advanced or aggressive disease have been shown to exhibit elevated NLR, which has been used to identify the patient populations at high risk for poor PFS and OS.[13] Although NLR has been investigated as a prognostic tool for patients with lung cancer, majority of the previous studies have been retrospective, have had significant heterogeneity in their findings, and have focused on inoperable nonsmall-cell lung cancers.[14]

Studies have shown that change in NLR (ΔNLR) on pre- and postintervention blood test results is an independent prognostic factor for patients with colon cancer undergoing curative resection and those receiving targeted interventions for renal cell carcinoma.[15,16] Moreover, ΔNLR has been shown to be a significant predictor of mortality in a lung cancer resection cohort, although the analysis was limited to Stage I patients.[17] At present, there is uncertainty regarding timing of ΔNLR and its utility; large effect findings may influence decisions regarding the use of adjuvant chemotherapy.

The present multicenter prospective study evaluated the prognostic potential of two inflammatory biomarkers, NLR and ΔNLR, to determine their utility in the risk stratification of patients with lung cancer undergoing definitive resection.

Methods

A total of 345 consecutive patients who underwent surgical resection for lung cancer at one of three Victorian Comprehensive Cancer Centre hospitals - Peter MacCallum Cancer Centre, The Royal Melbourne Hospital, and St. Vincent's Hospital Melbourne - were included in a prospectively maintained database. Patients who underwent palliative resection, aborted procedures, or had mesothelioma were excluded. Complete patient demographics, Eastern Cooperative Oncology Group status, and preoperative and postoperative blood test results were recorded. Tumor histopathology was recorded and grouped by stage utilizing the AJCC classification.[18]

NLR was calculated from preoperative blood test results (NLR_p) obtained within a month before surgery. ΔNLR at postoperative day 1 (ΔNLR_1) and day 2 (ΔNLR_2) was calculated using NLR_p and postoperative day 1 (NLR_1) and day 2 (NLR_2) blood test results. OS and PFS were determined utilizing follow-up data starting from the time of surgery.

Statistical analysis

Optimal cutoff values for elevated NLR were identified by calculating the maximally selected rank statistic,[19] subsequently identifying a cut-off of 4.54 for NLR. Associations between NLR, NLR_1, and NLR_2 and OS and PFS were determined using a univariate Cox proportional hazards model that included demographic and operative variables featured in Table 1. Adjusted hazard ratios (HRs) were then generated by inputting the significant covariates from the univariate analysis into a multivariate model. $P < 0.05$ indicated nominal statistical significance. The Bonferroni correction was then applied to adjust for multiple comparisons, with $P < 0.0083$, indicating statistically significant multivariate modeling. Survival curves were generated using the Kaplan–Meier method. All statistical analyses were performed using R Foundation for Statistical Computing, Vienna.[20]

This study was approved by the Peter MacCallum Cancer Centre Human Research Ethics Committee (HREC 19/135R).

Results

Population

General patient characteristics are shown in Table 1 and Appendix Table 1. Between 2000 and 2019, 345 patients (59% males; median age, 65.5 years) underwent surgical resection for lung cancer and had the required study investigations. The most common

histological subtype was adenocarcinoma (67%), followed by squamous cell carcinoma (24%), while 58% of the patients were AJCC Stage I. The most common surgical procedure was lobectomy (76%). A majority of the patients did not receive neoadjuvant treatment (90%). Postoperatively, 42% and 35% received radiotherapy and chemotherapy, respectively.

The median follow-up duration was 880 days (interquartile range, 1406).

Overall survival

Univariate analysis showed that preoperative NLR >4.54 was significantly associated with risk of death (HR 1.8, 95% confidence interval [CI] 1.2–2.6; $P < 0.01$) [Figure 1]. Day 1 and day 2 postoperative NLR were also significant prognostic indicators for mortality [$P < 0.01$; Table 2]. Multivariate analysis confirmed that all three indicators were statistically significant independent markers of increased mortality [$P < 0.01$; Table 3]. ΔNLR day 1 and day 2 after surgery were found to have no statistically significant prognostic value.

Progression-free survival

Univariate analysis revealed that preoperative NLR >4.54, as well as NLR day 1 and day 2 after surgery [$P < 0.05$; Table 4], was a significant prognostic indicator for disease progression [HR 1.7, 1.2–2.3; $P < 0.01$; Figure 2]. Multivariate analysis found preoperative NLR to be an independent prognosticator of cancer recurrence [HR, 1.65, 95% CI, 1.17–2.32; $P < 0.01$; Table 5].

Discussion

The present study demonstrated that preoperative NLR >4.54 was associated with poor OS and PFS among patients with lung cancer who underwent surgical resection even after multivariate adjustment, whereas ΔNLR was not associated with both OS and PFS.

NLR, an inexpensive test readily available from routine diagnostic blood tests, has been shown to improve the prognostication and risk stratification of individuals with a variety of cancers.[13] While the specific mechanism for this association has yet to be elucidated, NLR forms a hematological marker of systemic inflammation and appears more likely to be present in patients who are at increased risk for cancer recurrence or poor postoperative outcomes.[13]

Isolated neutrophilia has been associated with poor outcomes among patients with various types of cancer, including in lung cancer.[21] Although a definitive explanation for this association has still been lacking, hypothesized contributing factors include paraneoplastic production of myeloid growth factors by cancer cells and neutrophil-induced "tumor shedding."[21,22]

Table 1: General patient characteristics (*n*=345)

Characteristic	N
Gender	
Male/female	204/141
Age	65.5±6.5 IQR
Curative margins (%)	73.0
Histological subtype	
Adenocarcinoma	234
Squamous cell	85
Large cell undifferentiated	13
Neuroendocrine	9
Small cell	4
AJCC Stage	
1/2/3/4	202/54/64/25
ECOG	
0/1/2/3/4	135/186/17/6/1
Surgical treatment	
Lobectomy	263
Pneumonectomy	27
Wedge	44
Other cancer excision (*)	11
Neoadjuvant	
Chemotherapy/radiotherapy/none	1732/313
Adjuvant	
Chemotherapy/radiotherapy/none	124/145/76

*Other cancer excisions: Carinal resection, 2 Partial lobectomy, 5 Bronchial tumor removal, 1 Lymphadenectomy, 2 Debulking of mediastinal mass, 1, AJCC=Australian Joint Committee on Cancer Staging, ECOG=Eastern Cooperative Oncology Group, IQR=Interquartile range

Table 2: Univariate prognostic factors overall survival

Variable	HR	95% CI	P
NLR_p	1.8	1.2–2.6	<0.01
NLR_1	1.8	1.2–2.8	<0.01
NLR_2	1.9	1.2–3	<0.01
ΔNLR_1	1.4	0.94–2.1	0.1
ΔNLR_2	0.8	0.51–1.2	0.32
Sex: Male versus female	1.7	1.2–2.6	<0.01
Age>65.5 (median)	1.62	1.25–1.99	0.01
AJCC stage			
I	1	N/A	N/A
II versus I	1.23	0.65–1.81	0.48
III versus I	2.57	2.13–3.01	<0.01
IV versus I	1.48	0.84–2.12	0.23
ECOG			
1	1	N/A	N/A
2 versus 1	2.17	1.69–2.65	<0.01
3 versus 1	3.84	3.11–4.57	<0.01
4 versus 1	5.85	4.87–6.83	<0.01
5 versus 1	N/A	N/A	N/A

NLR=Neutrophil–lymphocyte ratio, AJCC=Australian Joint Committee on Cancer Staging, ECOG=Eastern Cooperative Oncology Group, CI=Confidence interval, HR=Hazard ratio, N/A=Not available

Lymphopenia exerts the same effect in raising NLR as increased neutrophil count. Lymphopenia has been associated with poor patient outcomes among patients with lung cancer and other solid organ cancers, such as renal cell carcinoma.[23,24] To our knowledge, there has been

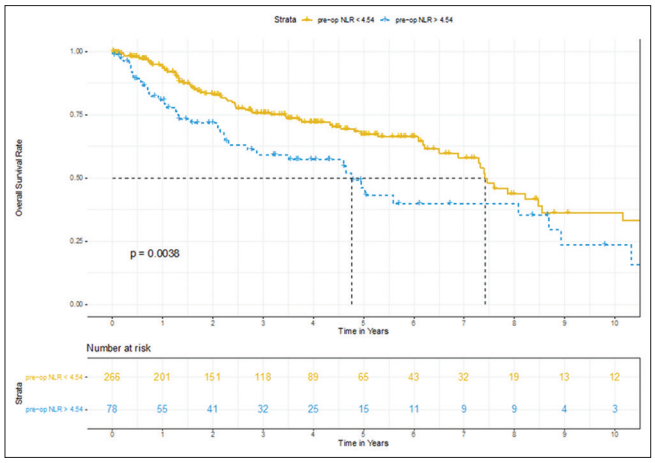

Figure 1: Kaplan–Meir curve of overall survival for preoperative neutrophil–lymphocyte ratio

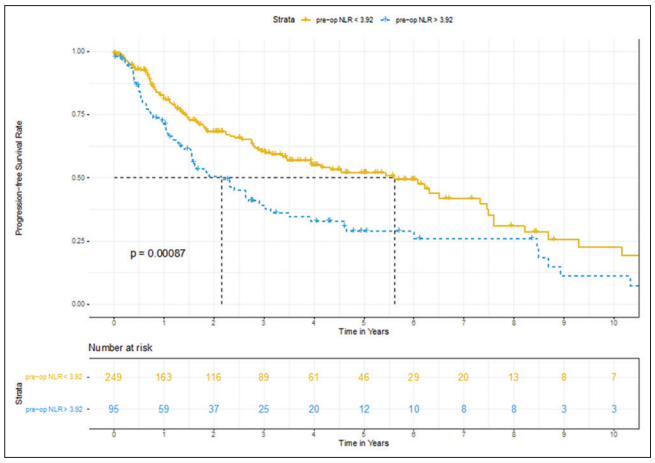

Figure 2: Kaplan–Meir curve of progression-free survival for preoperative neutrophil–lymphocyte ratio

no evidence of an association between lymphopenia and poor postoperative outcomes among surgically managed patients with cancer, highlighting a potential area for future research. Conversely, the presence of tumor infiltrating lymphocytes has been associated with improved outcomes among patients with nonsmall-cell lung carcinoma.[25]

Studies have demonstrated that NLR is a more powerful predictor of OS than neutrophil count or lymphocyte count alone.[26] While the exact threshold for NLR has varied between studies, it typically lies between >3 and > 5.[13] Despite the heterogeneity of NLR thresholds in the past research, there has been a clear association between increased NLR and poor outcomes in cancer surgery. The NLR of 4.54 utilized herein was calculated using maximally selected rank statistics and falls within previously established NLR thresholds.

The present study also explored ΔNLR, another hypothesized marker of systemic inflammation, utilizing preoperative and day 1/day 2 (D1/D2) blood test results. We utilized ΔNLR calculated from D1/D2 blood test results as this reflects real-world practice, these tests are routinely collected in the immediate postoperative period and significant findings may have influenced decisions regarding adjuvant treatment. No significant association was found in our cohort. A previous investigation by Jin *et al*. had found ΔNLR to be prognostic marker in lung cancer, although the study was limited to a small retrospective cohort of Stage I patients who underwent surgical resection.[17] Perhaps importantly, a major difference in design between the present study and Jin *et al*.'s study was the acquisition of postoperative NLR at the 1-month postoperative mark rather than day 1. Their reasoning was that most patients exhibit elevated NLRs during the postoperative inflammatory state immediately following surgery, potentially limiting the utility of a day 1 postoperative NLR.[17]

A key limitation of our cohort is its size. Although our cohort was sufficiently large to determine statistical significance, a larger sample size would allow for greater confidence in the findings and may have provided statistically significant results for other markers, such as ΔNLR. A larger cohort may have allowed for analysis of the specific TNM subgroups; the present study lacked the power to assess outcomes at this resolution.

The present study recruited patients across a 19-year period, encompassing a shift in the treatment strategies for lung cancer. New modalities such as neoadjuvant chemotherapy and radiotherapy were included in multi and univariate analysis, controlling for major treatment changes across this time period. Despite this, we cannot fully exclude the presence of other unaccounted for time-dependent covariates which may alter the estimate of prognostic significance of NLR.

A final limitation is that our cohort reflects only operatively managed patients. While surgery remains a primary treatment modality for lung cancer, select patients with locally advanced or metastatic cancer may be treated with chemotherapy or radiotherapy alone, and this study does not assess NLR's prognostic utility in this group.

Further research areas include investigation of biomarkers such as platelet–lymphocyte ratio and monocyte–lymphocyte ratio, and these may, with NLR, form a panel of readily available biomarkers for risk stratification of lung cancer patients. Future research with a larger cohort is required to further characterize patients not treated surgically and to evaluate patients in their specific TNM subcategories.

Current guidelines have recommended adjuvant chemotherapy for patients with Stage IIa, IIB, and IIIA disease. Although adjuvant chemotherapy is not routinely recommended for patients with Stage Ia and IB disease,

Table 3: Multivariate prognostic factors for overall survival

Variable	HR	95% CI	*P*
NLR_p	1.96	1.28–3	<0.01
NLR_1	1.71	1.09–2.70	<0.01
NLR_2	2.25	1.28–3.97	<0.01
Sex male	1.76	1.13–2.74	0.01
Age>65	1.72	1.13–2.59	0.01
Postoperative radiation	1.13	1.04–9.32	0.04
ECOG			
2	0.6	1.11–3.03	0.02
3	1.51	2.02–10.20	<0.01
4	2.23	2.88–30.39	<0.01

NLR=Neutrophil–lymphocyte ratio, ECOG=Eastern Cooperative Oncology Group, CI=Confidence interval, HR=Hazard ratio, N/A=Not available

Table 4: Univariate prognostic factors progression-free survival

Variable	HR	95% CI	*P*
NLR_p	1.7	1.2–2.3	<0.01
NLR_1	1.6	1.2–2.2	<0.01
NLR_2	1.5	1–2.1	0.04
ΔNLR_1	1.4	0.97–1.9	0.07
ΔNLR_2	0.9	0.62–1.3	0.6
Sex: Male versus female	1.2	0.87–1.6	0.28
Age>65.5 (median)			
AJCC Stage			
I	1	N/A	N/A
II versus I	0.86	0.382–1.34	0.54
III versus I	0.43	0.07–0.813	<0.01
IV versus I	0.9816	0.377–1.587	0.95
ECOG			
1	1	N/A	N/A
2 versus 1	1.467	1.1–1.835	0.04
3 versus 1	2.249	1.6–2.9	0.01
4 versus 1	4.405	3.54–5.27	<0.01

NLR=Neutrophil–lymphocyte ratio, ECOG=Eastern Cooperative Oncology Group, CI=Confidence interval, HR=Hazard ratio, N/A=Not available

Table 5: Multivariate prognostic factors progression-free survival

Variable	HR	95% CI	*P*
NLR_p	1.65	1.17—2.32	<0.01
Postoperative radiation	2.34	1.95–2.72	<0.01
Postoperative chemotherapy	1.52	1.16–1.87	0.02

CI=Confidence interval, HR=Hazard ratio, NLR=Neutrophil–lymphocyte ratio

patients with Stage I disease should be referred to a medical oncology department for further consideration if clinically appropriate.[27,28] While prognostic biomarkers, such as NLR, may improve the risk stratification of patients, further research should be conducted to determine whether the clinical use of NLR to guide treatment decisions would promote improved patient outcomes.

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Conflicts of interest
There are no conflicts of interest.

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Appendix

Appendix Table 1: Complete general patient characteristics (n=345)

Characteristic	*N*
Gender	
Male	204
Female	141
Age	Median 65.5, IQR±6.5
Curative margins (%)	73.0
Histological subtype	
Adenocarcinoma	234
Squamous cell	85
Large cell undifferentiated	13
Neuroendocrine	9
Small cell	4
AJCC Stage	
1/2/3/4	202/54/64/25
ECOG	
0/1/2/3/4	135/186/17/6/1
Surgical treatment	
Pneumonectomy	27
Lobectomy	263
Wedge	44
Other cancer excisions*	11
Neoadjuvant	
Preoperative chemotherapy	17
Preoperative radiotherapy	32
No neoadjuvant	313
Adjuvant	
Postoperative chemotherapy	124
Postoperative radiotherapy	145
Laterality	
Left	142
Right	203
Diabetes	49
CKD	16
Cardiovascular comorbidity	138
Respiratory comorbidity	115
Neoplastic comorbidity	118
Smoking	
Never	55
Current	54
Past	236
Age started smoking (median, IQR)	16±4.75
Average pack-years of cohort (median, IQR)	43±15
Average cigarettes per day	20±7.5
Marijuana use (ever)	322
Symptomatic	203 were, 142 were not
Ethnicity	
White	300
Asian	2
East Asian	28
South Asian/Indian	3

(Contd)

Appendix Table 1: (Continued)

Characteristic	*N*
Aboriginal/Torres straight	3
Pacific Islander/Maori	1
African	1
Mixed race	7
Loss of weight (%)	309
0–10	309
11–15	31
>15	4

*Other cancer excisions: Carinal resection, 2; Partial lobectomy, 5; Bronchial tumor removal, 1; Lymphadenectomy, 2; Debulking of mediastinal mass, 1. AJCC=Australian Joint Committee on Cancer Staging, ECOG=Eastern Cooperative Oncology Group, CKD=Chronic kidney disease, IQR=Interquartile range