Clinical impact of neutrophil-to-lymphocyte ratios in the blood and bronchoalveolar lavage fluid in patients with lung cancer

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Introduction

Various cancer-associated inflammatory biomarkers have been examined over the past decade, to refine treatment stratification of patients with cancer and predict survival. Notably, the neutrophil to lymphocyte ratio of peripheral blood (pbNLR), which is a readily available and inexpensive systemic inflammatory biomarker, has been established. There is a consensus that a high pbNLR is correlated with adverse overall survival (OS) in various cancers, including lung cancer.

Bronchoalveolar lavage (BAL) is a common, easily and safely performed diagnostic/therapeutic procedure for all lung disease patients, even those with acute illness. In particular, differential cell counts of BAL fluid provide useful information for diagnosing of various interstitial lung diseases (ILD) and evaluating the lung microenvironments of the lower respiratory tract. Furthermore, BAL fluid is in direct contact with the lung lesion, unlike other body fluids. Thus, the NLR of BAL fluid (bNLR), which is easily calculated based on differential cell counts, may provide important information on local inflammation of lung tumor origin. However, no study has reported on the clinical utility of the bNLR for patients with lung cancer. Only one study showed that the bNLR is associated with poor prognosis in patients with idiopathic pulmonary fibrosis (IPF).

Accordingly, we questioned whether the bNLR in patients with lung cancer has prognostic significance, like the pbNLR. To address this question, we prospectively obtained BAL fluid before other procedures were performed in patients with peripheral lung tumors undergoing bronchoscopy, to investigate the prognostic impact of the bNLR, and conducted a retrospective review of the prospectively collected data.

Materials and Methods

1. Study design and patients: We have been collecting BAL fluid during bronchoscopy of patients with suspected lung cancer or progression thereof at our institution since 2010. The BAL fluid is preferentially obtained before any other procedures, such as brushing, washing, biopsy, or aspiration, from the target tumors of these patients. The eligibility criteria were as follows: availability of a standard chest radiograph and chest CT before bronchoscopy; presence of an invisible endobronchial tumor (normal bronchial system or bronchial narrowing due to extrinsic compression with normal mucosa) and BAL fluid obtained from the target tumor during bronchoscopy before any other procedure; a definitive pathological diagnosis of lung cancer established by any diagnostic procedure other than bronchoscopy; no evidence of infection, such as bacteria, tuberculosis, or viruses, in the blood, sputum, or bronchial samples; and no use an inhaled corticosteroid or systemic steroid, and no chemotherapy or radiotherapy at least 1 month before bronchoscopy. Patients were excluded if they had a history of another malignancy within the previous 5 years or other diseases associated with systemic inflammation, such as a rheumatic disease or a connective tissue disorder.

2. Bronchoalveolar lavage processing: All bronchoscopy procedures were performed by the same pulmonologist, with extensive bronchoscopy experience, using several different video bronchoscopes (models BF-1T260, F260, and 6C260; Olympus, Tokyo, Japan) under local anesthesia (2% lidocaine spray) and mild conscious sedation with midazolam. BAL was performed according to the guidelines for the standardization of BAL.
The total and differential cell counts of BAL fluid were performed by an experienced laboratory medicine physician. Mycobacterial culture, tuberculosis polymerase chain reaction, cytology, and/or bacterial, fungal, and viral cultures of BAL fluid were performed.

3. Statistical analysis: The optimal cutoff values for the pbNLR and bNLR were determined using maximally selected rank statistics. These were calculated using the 'maxstat' package in R software, version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Table 1. Baseline characteristics according to the NLRs in bronchoalveolar lavage fluid

Variables	No. (%) n=48	NLR of BAL fluid Low	NLR of BAL fluid High	p value
Age				0.342
<65	21 (57.6)	9	12	
≥65	27 (42.4)	8	19	
Sex				0.054
Male	32 (66.7)	8	24	
Female	16 (33.3)	9	7	
Smoking				0.008
Current+Former	29 (60.4)	6	23	
Never	19 (39.6)	11	8	
EGOG PS				0.382
0-1	27 (56.3)	11	16	
2-4	21 (43.7)	6	15	
Histology				0.389
ADC	33 (68.7)	13	30	
SQC	9 (18.7)	3	6	
Others NSC	3 (6.3)	0	3	
SCC	3 (6.3)	1	2	
TNM stage				0.223
I-II	12 (25.0)	6	6	
III-IV	36 (75.0)	11	25	
pbNLR				0.032
Low (≤ 2.03)	18 (35.6)	10	8	
High (> 2.03)	30 (64.4)	7	23	
Hemoglobin (g/dl)				0.575
< 12.0 (13.1)	28 (58.3)	9	19	
≥ 12.0 (13.1)	20 (41.7)	8	12	
Platelet (10^9/L)				0.999
< 150	6 (12.5)	2	4	
≥ 150	42 (87.5)	15	27	
CRP (mg/dl)				0.342
≤ 0.5	21 (37.9)	9	12	
> 0.5	27 (62.1)	8	19	
Albumin (g/dl)				0.139
< 3.5	18 (37.5)	4	14	
≥ 3.5	30 (62.5)	13	17	
LDH (IU/L)				0.650
≤ 211	6 (43.8)	3	3	
> 211	32 (56.2)	11	21	

Table 2. Univariate and multivariate analyses of factors predictive of overall survival (OS) in all patients

Variables	Univariate analysis MST, day	Univariate analysis 95% CI	Univariate analysis p value	Multivariate analysis HR	Multivariate analysis 95% CI	Multivariate analysis p value
Age			0.370			
<65	704	442-966				
≥65	220	0-661				
Sex			0.322			
Male	270	0-655				
Female	1035	351-1719				
Smoking			0.028			
Current+Former	220	67-373				
Never	1087	222-1952				
EGOG PS			<0.001			
0-1	1450	596-2304				
2-4	107	26-188				
Histology			0.144			
ADC	642	0-1348				
SQC	616	0-1279				
Other NSC	113	0-255				
SCC	629	0-1620				
TNM stage			0.001			0.002
I-II	2605	1171-3439		ref.		
III-IV	262	4-519		6.24	1.90-20.43	
pbNLR			<0.001			0.009
≤ 2.03	2341	1591-3091		ref.		
> 2.03	208	53-363		4.45	1.45-13.72	
bNLR			0.020			0.008
≤ 0.2	1087	411-1763		ref.		
> 0.2	220	51-389		3.72	1.40-9.89	
Hemoglobin (g/dl)			0.106			
< 12.0	208	50-366				
≥ 12.0	809	0-2254				
Platelet (10^9/L)			0.158			
< 150	136	0-740				
≥ 150	629	265-993				
CRP (mg/dl)			<0.001			0.029
≤ 0.5	1619	198-3040		ref.		
> 0.5	140	25-255		2.90	1.12-7.53	
Albumin (g/dl)			0.014			
< 3.5	1035	511-1559				
≥ 3.5	140	0-337				
LDH (IU/L)			0.207			
≤ 211	704	0-1480				
> 211	262	0-582				

Figure 1. Kaplan-Meier curves of OS according to (a) the NLR in BAL fluid, and (b) the NLR in peripheral blood
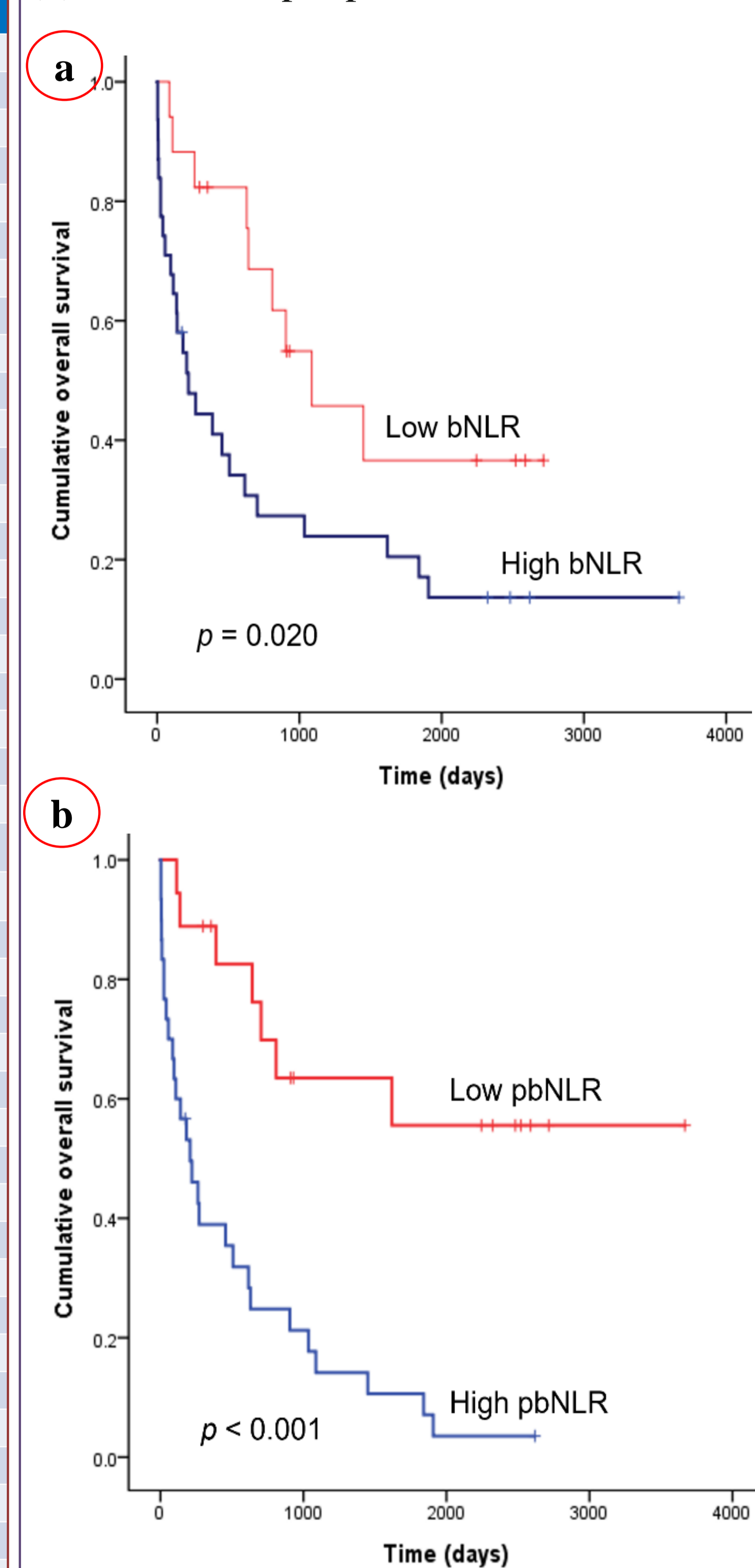
Conclusions

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In conclusion, similar to the pbNLR, a high bNLR value was associated with a poor prognosis in patients with lung cancer. Although further validation studies using larger cohorts are warranted to generalize our findings, the results suggest that the bNLR has potential as a readily available and cost-effective prognostic factor in patients with several lung diseases, including lung cancer.