Neutrophil/lymphocyte ratio and its association with survival after complete resection in non–small cell lung cancer

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Objective: Increasing neutrophil/lymphocyte ratios on preoperative blood tests have been associated with worse survival after resection of colorectal cancer. We sought to determine factors associated with increasing neutrophil/lymphocyte ratios and the stage-adjusted prognostic effect in patients undergoing resection for non–small cell lung cancer.

Methods: We performed a retrospective review of patients undergoing complete resection for non–small cell lung cancer between 1999 and 2005. Data acquisition was through patient medical records, blood results recorded on admission before surgical intervention, and follow-up by National Health Service database searches and hospital records. Cox proportional hazards regression was used to estimate the effect of neutrophil/lymphocyte ratio on stage-adjusted survival.

Results: During the study period, 178 patients underwent pulmonary resection. Of 177 patients, the majority were male 104 (59%), with a mean age of 63 years (standard deviation, 10 years). The median follow-up time was 29 months (interquartile range, 8–56 months), and overall survival was 83% and 54% at 1 and 5 years, respectively. Higher stage was the only factor found to be associated with increasing neutrophil/lymphocyte ratios ($P = .019$). Total white cell count ($P = .990$) and neutrophil count ($P = .490$), age ($P = .290$), and cell type ($P = .490$) were not significant predictors of mortality. On multivariable analysis after adjusting for stage, increasing neutrophil/lymphocyte ratios (hazard ratio, 1.10; 95% confidence interval, 1.03–1.17; $P = .004$) remained an independent prognostic indicator.

Conclusions: Increasing preoperative neutrophil/lymphocyte ratios are associated with higher stage but remain an independent predictor of survival after complete resection for primary lung cancer and are a potential biomarker to stratify high risk of death in patients with stage I disease.

Currently, joint guidelines issued by Cancer Care Ontario and the American Society of Clinical Oncology do not recommend the use of adjuvant chemotherapy in patients with completely resected stage I lung cancer.[1] Uniformly good survival in patients with stage I disease is not always the case because sophisticated, expensive, and not widely available techniques, such as tumor gene expression profiling, are able to substratify patients with early-stage cancer into high- and low-risk subsets.[2]

The purpose of this study was to determine the factors associated with increasing neutrophil/lymphocyte ratios (NLRs) and the relationship to survival in patients with non–small cell lung cancer to evaluate the discriminating value of the NLR to stratify patients with stage I disease at high risk of death.

MATERIALS AND METHODS

The chairman of the ethics committee approved this study and waived the need for ethics review. This study was conducted on patients operated on by a single surgeon (PG) between 1999 and 2005 and included all patients with non–small cell lung cancer who had undergone complete resection. We excluded any patients with coexistent hematologic disorders or known active infection at the time of surgical intervention to ensure that the white cell count was representative of a normal baseline value.

Data Acquisition

Data were compiled from individual patient medical case notes, electronic patient records (for laboratory results), and pathology reports. Demographics and serum values for the NLR were measured on the day before the operation to ascertain the baseline values for neutrophil and lymphocyte counts. Survival status was determined from the date of last follow-up in a hospital outpatient clinic or general practitioner clinic. Mortality status was documented from patient records and the National Health Service (United Kingdom) strategic tracing service.

Statistical Analysis

Categorical data are presented as frequencies (percentages) and continuous data as means with standard deviations or medians with interquartile ranges. Regression analysis was used to ascertain factors associated with increasing NLRs, and logarithmic transformation of the NLR was required to satisfy distributional assumption required for linear regression.

Receiver operating characteristic plots were constructed in the stage I subset of patients to determine the joint maximum sensitivity and specificity of a threshold value to stratify patients at high risk of death.

Actuarial survival was estimated by using the Kaplan–Meier method, and differences were tested with the log-rank test. Increasing values of

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Abbreviation and Acronym
NLR = neutrophil/lymphocyte ratio

NLR were expressed in tertiles to retain sufficient numbers per group for comparison. Cox proportional hazards regression was used to ascertain the individual contribution of factors associated with survival and to compare the stage-adjusted survival. Statistical analyses were performed with Stata version 9.2 (StataCorp, College Station, Texas) and R version 2.4.1 (R Core Development Team, Vienna, Austria).[3]

RESULTS

From January 1, 1999, to December 31, 2005, a total of 178 patients underwent surgical resection for non–small cell lung cancer. We excluded 1 patient with leukemia, leaving 177 suitable for inclusion. Systematic nodal dissection was undertaken in all cases. The mean age of the cohort was 63 years (standard deviation, 10 years), and 104 (59%) were men. The baseline characteristics, extent of operation, and pathologic stage are presented in Table 1. Follow-up was complete, with a median time to follow-up of 29 months (interquartile range, 8–56 months) and a 1- and 5-year overall survival of 83% and 54%, respectively.

Determinants of Increasing NLR Status

On regression analysis, neither age ($P = .259$), sex ($P = .786$), nor smoking were associated with increasing NLRs. Increasing overall pathologic stage ($P = .019$), as assessed by means of likelihood ratio testing, was the only variable identified to be associated with increasing NLRs.

Predictors of Survival

On univariable Cox regression modeling, neither total white cell count ($P = .990$) nor neutrophil count ($P = .490$) was significantly associated with risk of death. Increasing lymphocyte count was observed to be associated with a lower hazard ratio for death at 0.62 ($P = .012$), and increasing NLRs were observed to be associated with an increasing hazard ratio of death at 1.10 ($P = .001$, Figure 1). Hazard ratios of the covariates explored on univariable analysis are presented in Table 2.

On multivariable modeling, increasing NLRs were independent of pathologic stage (Table 3). The joint estimate of the effect per single unit increase in NLR after adjusting for pathologic stage was a hazard ratio of 1.10 (95% CI, 1.03–1.17; $P = .005$).

Discrimination in Stage I Survival

In the 83 patients with stage I disease, an NLR value of 3.81 corresponded to the maximum joint sensitivity and specificity on the receiver operating characteristic plot. When applied to a Kaplan–Meier model, a clear distinction in survival was obtained ($P < .001$, Figure 2).

TABLE 1. Baseline characteristics, operation extent, and stage

	Total
No.	177
Age, y (SD)	63 (10)
Male, n (%)	104 (59)
Right-sided resection, n (%)	95 (54)
Mean white cell count, $\times 10^9$ (SD)	9.16 (3.92)
Mean neutrophil count, $\times 10^9$ (SD)	6.32 (3.61)
Mean lymphocyte count, $\times 10^9$ (SD)	1.95 (0.79)
Median neutrophil/lymphocyte ratio (IQR)	3.13 (2.08–4.36)
Operation	
Pneumonectomy, n (%)	31 (18)
Lobectomy, n (%)	128 (72)
Bilobectomy, n (%)	14 (8)
Segmentectomy, n (%)	4 (2)
Histology	
Squamous, n (%)	56 (32)
Adenocarcinoma, n (%)	86 (49)
Large cell, n (%)	16 (9)
Mixed, n (%)	5 (3)
Other, n (%)	14 (8)
Pathologic stage	
IA, n (%)	25 (14)
IB, n (%)	58 (33)
IIA, n (%)	7 (4)
IIB, n (%)	38 (21)
T2 N1	28 (16)
T3 N0	10 (6)
IIIA, n (%)	38 (21)
T1-3 N2	33 (19)
T3 N1	5 (3)
IIIB, n (%)	7 (4)
T4	7 (4)
IV, n (%)	4 (2)

SD, Standard deviation; *IQR*, interquartile range.

DISCUSSION

The results of our study suggest that increasing NLRs are associated with increasing tumor stage but exert an independent effect on survival in patients with completely resected non–small cell lung cancer, even after adjustment for stage.

The NLR, an inexpensive, reproducible, and widely available blood test, has been found to be an important indicator of adverse prognosis in colorectal[4,5] and gastric[6] cancers. Although the cause for the association between increasing NLRs and adverse outcome has not been elucidated, individually, a high neutrophil count has been reported as an adverse marker of prognosis in metastatic melanoma[7] and renal cell carcinoma,[8] and a low lymphocyte count has been reported as a marker of mortality in pancreatic cancer.[9]

Recently, an increasing neutrophil count has also been identified as an independent predictor of death in patients with advanced non–small cell lung cancer,[10] and neutrophils have been implicated in the promotion of aerogenous metastasis in patients with bronchioloalveolar carcinoma.[11] On its own, as an isolated measured variable, we did not find any

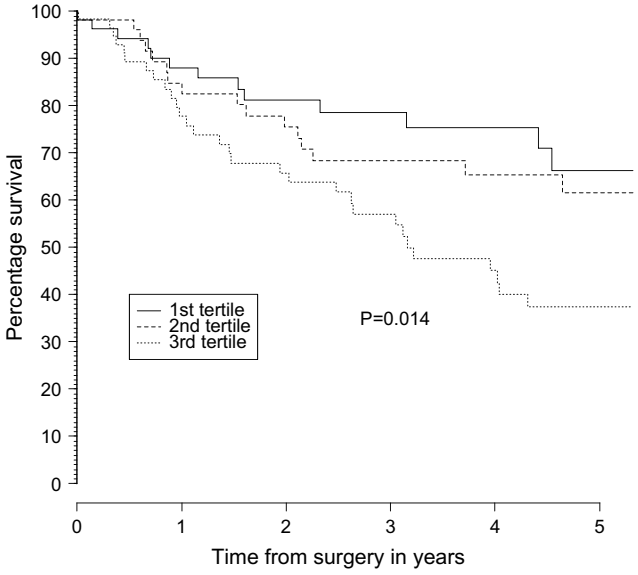

FIGURE 1. Survival by neutrophil/lymphocyte ratio tertiles.

association between the absolute value of the neutrophil count on survival after complete resection of early-stage non–small cell lung cancer; in part this might be due to statistical variation or simply the lack of a consistent relationship.

A low lymphocyte count is a recognized predictor of poor survival in patients with advanced cancer attributed to the fundamental role of lymphocytes in cell-mediated immunity with destruction of host cancer cells and has been found to be a predictive marker of response to chemotherapy.[12] Our results are consistent in this cohort of patients with early-stage lung cancer, even after complete resection, because higher preoperative lymphocyte counts were found to be associated with improved survival. It is plausible that host cell-mediated immunity continues to exert important effects on destruction of any residual tumor cells and micrometastases, despite complete resection of the main tumor. It will require a study of relapse patterns to assess the possible implications and mechanisms of NLRs.

In small cell lung carcinoma, after complete resection, high lymphocyte counts have been associated with improved survival, which is ascribed to the pivotal role of specific T-cell subsets (including tumor-infiltrating lymphocytes) in cytotoxic cell death and cytokine production that regulates proliferation and metastatic activity of tumor cells.[13]

The NLR, as a measure of the relative differences of the baseline neutrophil and lymphocyte counts, was discovered to be a more powerful predictor of death than either component alone or pathologic stage. On regression analysis, we demonstrated the association between stage and increased NLR ($P = .019$). However, it is not possible to distinguish cause from effect, increasing tumor burden might incite a neutrophil reaction, and certainly an association was also present between increasing absolute neutrophil counts and increasing pathologic stage ($P = .017$). Multivariable modeling, however, confirmed a more independent (and more powerful) effect than pathologic stage as a biomarker of poor prognosis. This has also been recently reported in advanced lung cancer, where a similar association was

TABLE 2. Univariable predictors of survival

Covariate	Hazard ratio	95% CI	*P* value
Neutrophil count, $\times 10^9$ mL*	1.02	0.96–1.09	.490
Lymphocyte count, $\times 10^9$ mL*	0.62	0.43–0.90	.012
Total white cell count, $\times 10^9$ mL*	1.00	0.94–1.07	.990
Neutrophil/lymphocyte ratio*	1.10	1.04–1.17	.001
N category			
N0	1.00	NA	NA
N1	2.06	1.13–3.74	.018
N2	1.99	1.09–3.62	.024
Stage			
I	1.00	NA	NA
II	1.59	0.84–3.03	.160
III	2.17	1.22–3.86	.009
IV	1.99	0.47–8.42	.350
Age (per additional year)	1.01	0.99–1.04	.290
Female sex	1.56	0.93–2.61	.089

CI, Confidence interval; *NA*, not applicable. *Per unit increase.

TABLE 3. Multivariable predictors of survival

Covariate	Hazard ratio	95% CI	*P* value
Neutrophil/lymphocyte ratio*	1.10	1.03–1.17	.005
Stage			(.126)†
I	1.00	NA	NA
II	1.23	0.62–2.45	.550
III	2.03	1.14–3.62	.017
IV	1.64	0.39–7.01	.500

CI, Confidence interval; *NA*, not applicable. *Per unit increase. †The overall contribution of stage was assessed by using the likelihood method.

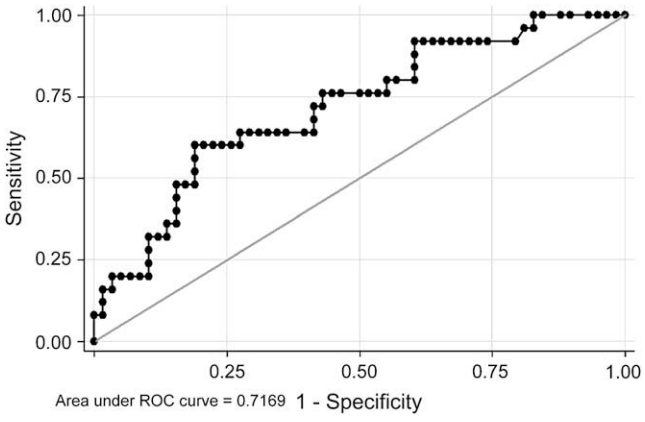

FIGURE 2. Survival of 83 patients with pathologic stage I disease. *NLR*, Neutrophil/lymphocyte ratio; *ROC*, receiver operating characteristic.

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observed. The index was presented as a reversed ratio (lymphocyte/neutrophil ratio), and lower scores were identified as an increasing independent predictor of death.[14]

Currently, joint guidelines issued by Cancer Care Ontario and the American Society of Clinical Oncology do not recommend the use of adjuvant chemotherapy in patients with completely resected stage I lung cancer,[1] citing little evidence of efficacy in these subgroups. The NLR is a potential biomarker to influence patient selection in this regard because it is almost universally available and adds no additional cost to routine preoperative workup in comparison with more sophisticated and expensive technologies.[2] Clearly further validation work and a feasibility study are required before it can be considered for clinical use.

CONCLUSIONS

Increasing preoperative NLRs are associated with higher stage but remain an independent predictor of survival after complete resection for non–small cell lung cancer and are a potential biomarker to stratify high risk of death in patients with stage I disease.

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