Hematology/Oncology and Stem Cell Therapy

Volume 16 | Issue 2 Article 10

Predicting if lung cancer will relapse—The role of neutrophil/lymphocyte ratio

Abigail Chan
Department of Medicine, Sinai Hospital of Baltimore, Baltimore, MD 21215, USA, abigail.chan.1@louisville.edu

Søren Bentzen
Department of Statistics, University of Maryland School of Medicine, Baltimore, MD 21201, USA

Amit Rout
Department of Medicine, Sinai Hospital of Baltimore, Baltimore, MD 21215, USA

Kenneth Miller
Department of Hematology and Medical Oncology, Sinai Hospital of Baltimore, Baltimore, MD 21215, USA

LETTER TO EDITOR

Predicting if Lung Cancer Will Relapse—The Role of Neutrophil/Lymphocyte Ratio

Abigail Chan [a,1,*], Søren Bentzen [b], Amit Rout [a,2], Kenneth Miller [c]

[a] Department of Medicine, Sinai Hospital of Baltimore, Baltimore, MD 21215, USA
[b] Department of Statistics, University of Maryland School of Medicine, Baltimore, MD 21201, USA
[c] Department of Hematology and Medical Oncology, Sinai Hospital of Baltimore, Baltimore, MD 21215, USA

Abstract

Objective/Background: **Baseline neutrophil/lymphocyte ratio (NLR), a surrogate marker for systemic inflammation and immunosuppression, is a well-studied prognostic marker in non-small cell lung cancer (NSCLC). This study tests if interim NLR is prognostic in NSCLC patients in remission.**

Methods: **This single-center, retrospective cohort study analyzed 131 NSCLC patients treated from 2010 to 2015 who achieved complete remission. NLR was calculated at baseline and from the first available blood sample during remission. Kaplan—Meier estimates of overall survival (OS) and time to recurrence were compared using the log-rank test for trend. Multivariable analysis was conducted using the Cox proportional hazards model.**

Results: **Of the 131 cases, 63 had subsequently recurred at the last follow-up. The mean age was 64 ± 10 years. Patients with stage I (35%), II (24%), and III (41%) were included. Histology were adenocarcinoma (60%), squamous cell (33%), and unspecified (7%). The majority of patients were smokers. For the univariate analysis interim NLR was binned into tertiles, NLR < 2, 2—4.08, and > 4.08. Of those with an interim NLR > 4.08, prognosis and recurrence risk were higher. In the multivariable analysis, remission NLR was strongly prognostic for OS ($p < .001$) as did patient's age ($p = .002$), but not stage, race, sex, and baseline NLR.**

Conclusions: **Our study found that interim NLR, obtained in remission, was strongly prognostic for OS and recurrence.**

Keywords: NSCLC, Neutrophil/lymphocyte ratio, Prognostic markers, Biomarkers

1. Introduction

Lung cancer continues to be a leading cause of cancer-related mortality. Despite surgical and medical advancements, prognosis remains poor. Reliable prognostic markers in non-small cell lung cancer (NSCLC) are few. The tumor, node, and metastasis (TNM) staging system and performance status are known indicators. However, sex, histology type, age, sarcopenia, and abnormal hematologic indices have been less prognostic [1,2]. Several studies have demonstrated the association of baseline neutrophil/lymphocyte ratio (NLR) and overall survival (OS) in several cancers [3]. In NSCLC, a high baseline NLR has been correlated with inferior OS, increased recurrence risk, and poorer treatment response in different modalities [4—8].

Although the biologic significance of the NLR has not been completely elucidated, it may crudely represent the tumor microenvironment (TME). The TME, composed of innate and adaptive immune cells and stromal components, modulates cancer

Abbreviations: ANC, absolute neutrophil count; ALC, absolute lymphocyte count; CBC, complete blood count; NLR, neutrophil/lymphocyte ratio; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; TME, tumor microenvironment; TNM, tumor, node, and metastasis

Received 17 April 2021; revised 4 August 2021; accepted 23 August 2021.
Available online 17 January 2023

* Corresponding author at: Department of Hematology/Oncology, University of Louisville, 529 S Jackson Street, Louisville, KY 40202, USA.
E-mail address: abigail.chan.1@louisville.edu (A. Chan).
[1] Present address: Department of Hematology/Oncology, University of Louisville, Louisville, KY 40202, USA.
[2] Present address: Department of Cardiology, Einstein Medical Center, Philadelphia, PA 19141, USA.

https://doi.org/10.1016/j.hemonc.2021.08.003

initiation, progression, and metastasis in sites of chronic inflammation. In the presence of immunosuppression, this response becomes heightened [9].

It remains to be clarified whether NLR during remission reflects the risk of subsequent cancer recurrence. Therefore, the purpose of this study is to evaluate the prognostic significance of an interim NLR in patients who achieved remission after receiving primary therapy.

2. Methods

2.1. Patient selection

A chart review was undertaken of NSCLC patients between January 1, 2010 and December 31, 2014 at the University of Maryland Greenebaum Cancer Center. The inclusion criteria were: (a) NSCLC based on pathologic examination, (b) clinical and pathological stage I A to III B based on TNM classification, (c) treated and followed up after remission, and (d) complete blood count (CBC) with differential counts at predetermined time points. Patients with incomplete laboratory data, those lost to follow-up, or received immunotherapy were excluded (Supplementary Figure S1).

2.2. Data collection

Baseline demographics data were retrieved from the electronic medical records. NLR was calculated by dividing the absolute neutrophil count with the absolute lymphocyte count. NLR values were obtained at initial evaluation and after having achieved clinical and radiographic remission. The most recent CBC available prior to treatment initiation was preferred. Hematologic data obtained while receiving corticosteroids or due to infective/inflammatory conditions were excluded. The oncologic endpoints were OS, time to recurrence, and progression-free survival (PFS). Patients, who did not reach the endpoint, were censored at the time of last follow-up.

2.3. Statistical analysis

OS and PFS were quantified by 2-year Kaplan–Meier estimates and compared between groups using the log-rank test or the log-rank test for trend, as appropriate. Multivariable analysis was conducted using the Cox proportional hazards model.

3. Results

3.1. Population

A total of 131 patients were included; 63 had subsequent lung cancer recurrence at the time of last follow-up. The mean age of patients was 64 years. Patients with stage I (35%), II (24%), and III (41%) were included, with a majority requiring multimodality therapy (60%). Surgical interventions included lobectomy, wedge resection, and segmentectomy depending on extent of cancer. Population was distributed evenly between Black and Caucasian race. Baseline demographics are shown in Supplementary Table S1.

3.2. Neutrophil/lymphocyte ratios

The median baseline and interim NLR were 2.6 (range, 0.6–34.0) and 3.1 (range, 0.5–20.5), respectively. The time from end of treatment, median (range), to the interim NLR was 9.2 (range, 2.2–66.7) months. The median duration of follow-up was 44 (range, 5.9–101) months.

For the univariate analysis, the interim NLR was binned into tertiles. The interim NLR was prognostic for OS ($p = .0004$) and PFS ($p = .032$), but not for 2-year progression free rate (Supplementary Table S2 and Fig. 1). In the multivariable analysis, the interim NLR remained strongly prognostic for OS ($p < .001$) as did patient's age ($p = .002$), but was not found to be prognostic for stage, race, sex, and baseline NLR (Table 1).

4. Discussion

In this study, interim NLR was strongly associated with 2-year OS and PFS in patients with both clinical and radiographic remission. The median time from end of treatment to interim NLR was 9.2 months, allowing for bone marrow recovery after treatment. Furthermore, we demonstrated that the interim NLR and age were independent prognostic markers.

NLR can serve as an indirect marker of inflammation and immunosuppression. Currently, there is no established threshold for an elevated NLR. A study involving more than 40,000 patients reported that a baseline NLR ≥ 4 was associated with worse OS, PFS, and disease-free survival, irrespective of cancer stage or site [3]. For this study, a similar threshold of > 4.08 was designated.

We aimed to do a longitudinal assessment of NLR in patients who achieved remission. Several studies have demonstrated the relationship of an

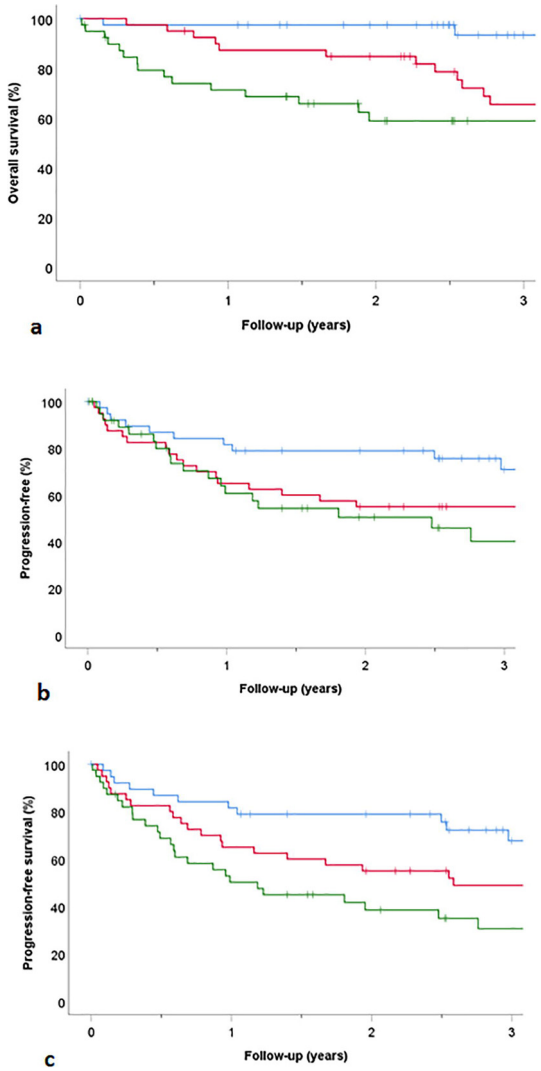

Fig. 1. Kaplan–Meier estimates of (a) overall survival, (b) progression-free rate, and (c) progression free survival. Legend: NLR tertiles of interim NLR < 2 (blue), NLR 2–4.08 (red), and NLR > 4.08 (green). Note. NLR = neutrophil/lymphocyte ratio. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

elevated baseline NLR with poor OS in multiple cancers, irrespective of treatment modality or disease stage [4–8]. This includes one with locally advanced NSCLC, demonstrating an inverse relationship between NLR value and OS after multimodality therapy [4]. In patients with completely resected stage I NSCLC, a high NLR was an independent predictor of recurrence but not OS [5]. Similar results were seen in three longitudinal studies that focused on NLR trends while on treatment with doublet chemotherapy, combination chemotherapy, and immunotherapy [10–12]. In contrast, the patients in our study were already in remission and were not receiving treatment, with a median time from end of treatment to the interim NLR of 9.2 months. At this time point, 48% of our study patients had recurrence, which is relatively short compared to a previous study showing median time to recurrence from surgery of 18.5 (range, 15–21.3) months [13]. One of the strengths of our study is an almost equal distribution between Blacks and Caucasians, with the former population usually underrepresented in clinical studies. Prior retrospective studies have reported possible racial differences in NLR levels [14]. There are several limitations to this study. As our study was a retrospective in nature, there was no standardized protocol for when to do the CBC. Unless documented clearly, our NLR values may have been confounded by inflammation and use of corticosteroids, which could elevate the ANC.

Table 1. Hazard Ratio for Patient with Value at 75th Percentile Compared to 25th Percentile of the Population Distribution of the Covariate.

	Hazard ratio	95% Confidence interval	*p*
Interim NLR	1.60	1.29–1.99	<0.001
Initial NLR	1.16	1.00–1.34	0.05
Age at diagnosis	2.32	1.35–3.96	0.002

Note. NLR = neutrophil/lymphocyte ratio.

5. Conclusions

Interim NLR obtained in remission was strongly prognostic for OS and recurrence. The results suggest that even subclinical disease promotes immunosuppression or alternatively that immunosuppression increases recurrence risk. NLR during remission may help identify NSCLC patients at high risk of recurrence and may thus be of value in surveillance of lung cancer survivors and in developing potential interventions in those with high NLR during remission.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hemonc.2021.08.003.

References

[1] Woodard GA, Jones KD, Jablons DM. Lung cancer staging and prognosis. Cancer Treat Res 2016;170:47–75.

[2] Holgersson G. Prognostic factors in non-small cell lung cancer (NSCLC). Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine 1359. Uppsala, 2017. p. 84.
[3] Templeton AJ, McNamara MG, Šeruga B, Vera-Badillo FE, Aneja P, Ocana A, et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. J Natl Cancer Inst 2014;106:dju124.
[4] Scilla KA, Bentzen SM, Lam VK, Mohindra P, Nichols EM, Vyfhuis MA, et al. Neutrophil-lymphocyte ratio is a prognostic marker in patients with locally advanced (stage IIIA and IIIB) non-small cell lung cancer treated with combined modality therapy. Oncologist 2017;22(6):737–42.
[5] Mizuguchi S, Izumi N, Tsukioka T, Komatsu H, Nishiyama N. Neutrophil-lymphocyte ratio predicts recurrence in patients with resected stage 1 non-small cell lung cancer. J Cardiothorac Surg 2018;13:78.
[6] Diem S, Schmid S, Krapf M, Flatz L, Born D, Jochum W, et al. Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) as prognostic markers in patients with non-small cell lung cancer (NSCLC) treated with nivolumab. Lung Cancer 2017;111:176–81.
[7] Bagley SJ, Kothari S, Aggarwal C, Bauml JM, Alley EW, Evans TL, et al. Pretreatment neutrophil-to-lymphocyte ratio as a marker of outcomes in nivolumab-treated patients with advanced non-small-cell lung cancer. Lung Cancer 2017;106:1–7.
[8] Sebastian N, Wu T, Bazan J, Driscoll E, Willers H, Yegya-Raman N, et al. Pre-treatment neutrophil-lymphocyte ratio is associated with overall mortality in localized non-small cell lung cancer treated with stereotactic body radiotherapy. Radiother Oncol 2019;134:151–7.
[9] Coussens LM, Werb Z. Inflammation and cancer. Nature 2002;420(6917):860–7.
[10] Derman BA, Macklis JN, Azeem MS, Sayidine S, Basu S, Batus M, et al. Relationships between longitudinal neutrophil to lymphocyte ratios, body weight changes, and overall survival in patients with non-small cell lung cancer. BMC Cancer 2017;17(1). https://doi.org/10.1186/s12885-017-3122-y.
[11] Li B, Wang S, Li C, Guo M, Xu Y, Sun X, et al. The kinetic changes of systemic inflammatory factors during bevacizumab treatment and its prognostic role in advanced non-small cell lung cancer patients. J Cancer 2019;10(21):5082–9.
[12] Labomascus S, Fughhi I, McDonald A, et al. Association of baseline and longitudinal low neutrophil-lymphocyte ratio (NLR) and high lymphocyte counts (LCs) with progression-free survival (PFS) and overall survival (OS) in real world advanced non-small cell lung cancer (aNSCLC) patients (pts) treated with nivolumab (nivo) or pembrolizumab (pembro). J Clin Oncol 2018;36:no. 15_suppl.
[13] Valdes M, Nicholas G, Goss GD, Wheatley-Price P. Chemotherapy in recurrent advanced non-small-cell lung cancer after adjuvant chemotherapy. Curr Oncol 2016;23(6):386–90.
[14] Ueberroth BE, Khan A, Zhang KJ, Philip PA. Differences in baseline characteristics and white blood cell ratios between racial groups in patients with pancreatic adenocarcinoma. J Gastrointest Cancer 2021;52(1):160–8.