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Prognostication of non–small cell lung cancer with concurrent chemoradiation treatment using neutrophil-to-lymphocyte ratio

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Purpose: We evaluated neutrophil-to-lymphocyte ratio (NLR) as a prognostic factor in patients with stage III unresectable non–small cell lung cancer (NSCLC) treated with concurrent chemoradiation (CRT). Furthermore, we examined neutrophil and lymphocyte changes to determine their contributions to NLR variation over time.

Materials and Methods: A retrospective review was performed that included 262 patients diagnosed with stage III unresectable NSCLC from 2005 to 2020 who received concurrent CRT with a 60 Gy or 66 Gy in 30 fractions radiotherapy regimen. Pre-CRT NLR, lymphocyte nadir NLR, post-CRT NLR at 1 month ± 2-week intervals up to 6 months relative to the end of CRT, and NLR fold-change were calculated. The primary endpoint was overall survival.

Results: Of the examined parameters, high NLR had the most consistently high prognostic value for poorer outcomes for all 3 endpoints in the 6-month period post-CRT, with the highest hazard ratios (HRs) at 3 to 4 months. This was associated with a decrease in neutrophils from 3 to 4 months, while NLR and lymphocytes were relatively stable. Several other parameters at 4 months, including individual cell counts and NLR fold-change (relative to the lymphocyte nadir), were associated with high HRs for mortality.

Conclusion: Our study suggests that a window of time at 3 to 4 months post-CRT exists for when NLR and related hematologic parameters demonstrate increased prognostic value. This period may represent an area for further investigation as a potential opportunity for risk stratification with possible implications for surveillance and treatment.

Keywords: Non-small-cell lung carcinoma, Chemoradiotherapy, Biomarkers, Prognosis

Introduction

Lung cancer has re-emerged as the most frequently diagnosed cancer, accounting for one in eight cancers globally, and remains the leading cause of cancer death worldwide, responsible for one in five cancer deaths [1]. Non–small cell lung cancer (NSCLC) is the most common histological type, accounting for about 85% of lung cancers [2]. Approximately 30% of NSCLC cases are locally advanced or stage III at diagnosis; the majority of stage III NSCLC cases are considered unresectable [3]. The most recent real-world data for patients with stage III unresectable NSCLC treated with the current standard of care of concurrent chemoradiation (CRT) with consolidation durvalumab as per PACIFIC have been reported 5-year overall survival (OS) to be 49.2% and progression-free survival to be 35.2% [4,5].

Despite advancements in treatment, outcomes for patients with unresectable, locally advanced NSCLC remain poor, highlighting the need for predictive and prognostic markers to better guide management strategies [6]. Systemic inflammation has emerged as an important contributory factor in cancer progression and treatment response [7]. In particular, markers of inflammation such as neutrophil-to-lymphocyte ratio (NLR), which are derived from routine blood tests, have garnered attention as potential prognostic indicators [8]. These markers reflect the activity of neutrophils and lymphocytes, both playing key roles in cancer progression [9]. Neutrophils can promote tumour progression through mechanisms including immunosuppression, angiogenesis, and cytokine-mediated invasion [10]. Conversely, lymphocytes have roles in adaptive immunity and may contribute to the effects of radiation (RT) toxicity [11]. As such, further assessment of these markers is needed to validate these biomarkers as tools for risk stratification.

Our project aims to evaluate prognostic factors including pre- and post-CRT NLR, in relation to survival outcomes in patients with unresectable, locally advanced NSCLC. Furthermore, we seek to explore the individual contributions of these ratio components to better understand the underlying mechanisms driving their prognostic value. Understanding the contributions of neutrophils and lymphocytes to NLR may offer insights into the biological mechanisms underlying NSCLC progression and treatment resistance. Ultimately, this research may aid in improving risk stratification, guiding treatment decisions, and enhancing personalized care for NSCLC patients.

Materials and Methods

1. Patients

We retrospectively reviewed 852 patients newly diagnosed with stage III NSCLC (American Joint Committee on Cancer [AJCC] 8th edition of the TNM classification) between 2005 and 2020, and who received concurrent CRT at British Columbia Cancer sites [12]. The inclusion criteria included: treatment with concurrent CRT using a 60 Gy or 66 Gy in 30 fractions RT regimen; histologically confirmed NSCLC; and neutrophil and lymphocyte counts performed before CRT. Exclusion criteria included evidence of acute infection, surgical resection, past malignancies within 5 years with ineligible histology (e.g., curatively treated basal, squamous cell carcinoma, or melanoma of the skin; or in situ carcinoma of the cervix remain eligible), past systemic steroid use, past chemotherapy, granulocyte colony-stimulating factor use, and tumor-related leukemoid reaction (white blood cell $> 50 \times 10^9$/L). After applying these criteria, 262 patients were included for analysis. This study was approved by the BC Cancer Research Ethics Board.

2. Chemoradiotherapy

Chemotherapy included cisplatin/etoposide, cisplatin/gemcitabine, cisplatin/pemetrexed, or carboplatin/paclitaxel. Radiotherapy was planned using three-dimensional conformal radiotherapy (3D-CRT), intensity-modulated radiotherapy (IMRT), or volumetric modulated arc therapy (VMAT) techniques, with RT doses of 66 Gy or 60 Gy in 30 fractions.

3. Neutrophil-to-lymphocyte ratio

The pre-CRT NLR was calculated from the nearest complete blood count (CBC) performed prior to the start of CRT. The lymphocyte nadir NLR was calculated from the on-treatment CBC demonstrating the lowest lymphocyte count. Post-CRT values were obtained at 1 month ± 2-week intervals up to 6 months after completion of CRT. NLR fold-change was calculated at each time point post-CRT, relative to pre-CRT and the lymphocyte nadir values. Platelet-to-lymphocyte ratio (PLR) was also assessed as a secondary, exploratory biomarker of systemic inflammation that has previously demonstrated mixed results regarding its prognostic value in stage III NSCLC [8,13-15].

4. Response and follow-up

The primary endpoint of OS was calculated from the CRT start date to the date of death from any cause or most recent follow-up using the Kaplan-Meier method. Locoregional progression–free survival (LRPFS) and distant metastasis–free survival (DMFS) were secondary endpoints. Distant metastasis was defined as any of the following: malignant pleural or pericardial effusion, pleural or pericardial nodules, separate tumor nodule(s) in a contralateral lobe, or any extrathoracic metastases. Locoregional progression was any progression not included by the definition of distant metastasis, as specified by the AJCC 8th edition of the TNM classification [12].

5. Statistical analysis

Maximally selected log-rank statistics were used to determine optimal cutoffs for the measured and calculated parameters at each time point for creating high and low groups for evaluating OS, LRPFS, and DMFS using the R package "maxstat" [16]. Bootstrap sampling of the cutoffs with 1,000 resamples was performed for OS at each time point and for each parameter as internal validation, with bias-corrected and accelerated confidence intervals. Multivariate Cox regression compared high and low groups of bloodwork parameters, adjusting for age, sex, stage, Eastern Cooperative Oncology Group (ECOG) performance status, history of smoking, number of cycles, chemotherapy protocol, and RT technique. Fine and Gray competing risks regression was applied to the multivariate analyses of LRPFS and DMFS. Benjamini-Hochberg adjustment was used to account for multiple hypothesis testing of several time points and parameter types within each assessed endpoint. Statistical significance was set at a threshold of a two-sided p-value <0.05. All statistical analyses were performed using R (R Foundation for Statistical Computing, Vienna, Austria, version 4.4.1) [17]. Other R packages used include "tidyverse" for analysis and visualization and "survival" for survival analysis [18,19].

Results

1. Patient and treatment characteristics

The median age was 64 years, ranging from 42 to 83 years (interquartile range [IQR], 59 to 70). Sex was approximately evenly split between males and females, with better prognosis for females across the three endpoints ($p = 0.005$, $p = 0.003$,, and $p = 0.037$ for OS, LRPFS, and DMFS, respectively) (Table 1). Median OS for the cohort was 30.1 months (95% confidence interval [CI], 24.3 to 42.8), while median LRPFS and DMFS were 20.6 months (95% CI, 16.3 to 27.0) and 17.7 months (95% CI, 14.7 to 22.8), respectively. There were 156 patients (59.5%) with stage IIIA, 93 patients (35.5%) with stage IIIB, and 13 patients (5.0%) with stage IIIC disease, with more advanced stage associated with worse prognosis. Most of the patients (89.3%) had an ECOG performance status of 0 to 1. Most of the cohort had a previous smoking history (94.3%), which was associated with increased mortality ($p = 0.017$). A total of 121 patients (46.2%) were diagnosed with adenocarcinoma and 55 patients (21.0%) were diagnosed with squamous cell carcinoma, with relatively similar outcomes across the three endpoints. The RT technique that patients most often received was 3D-CRT (54.2%), followed by VMAT (28.2%) and IMRT (17.6%), with similar outcomes between the techniques. Patients most often received cisplatin and etoposide chemotherapy (88.5%), with uneven sample sizes decreasing the generalizability of the findings for differences in outcomes in chemotherapy type. The median number of chemotherapy cycles was 4, ranging from 1 to 8 cycles (IQR, 2 to 6). Of note, our study did not include any patients who received durvalumab as part of their treatment.

2. Time course

Mean NLR increased by 3.35 from pre-CRT to the lymphocyte nadir. This was primarily driven by a 0.24-fold decrease in lymphocyte count (i.e., about one quarter of the original) (Fig. 1). Although neutrophil count also declined during this period, its reduction was less pronounced at 0.53-fold. Following the lymphocyte nadir, NLR decreased by 0.59-fold by 1 month post-CRT. However, NLR remained elevated relative to their pre-CRT levels. Similar changes were observed in platelet count, with less variation in PLR than NLR over time (S1).

Across all time points, several parameters measured around the 3 to 4-month mark post-CRT, including NLR fold-change (relative to the lymphocyte nadir), NLR, and individual cell counts were associated with the highest hazard ratios (HRs) for mortality (Fig. 2). The next most prognostic time point was around 6 months post-CRT. Notably, the differences at 4 months post-CRT were accompanied by a decrease in neutrophil count between months 3 to 4, while lymphocyte count remained stable (Fig. 1). These counts subsequently rebounded between months 5 and 6. In contrast, mean NLR did not show meaningful changes around the 3 to 4-month mark (the apparent discrepancy between the changes in mean NLR and the mean individual cell counts was due to cell count distribution amongst patients and the calculation of mean NLR compared to the ratio of mean cell counts, i.e., $[NLR_1 + \cdots + NLR_n] / n \neq$ [mean neutrophil count]/[mean lymphocyte count]).

3. OS according to NLR

NLR demonstrated the most consistent and robust prognostic value for OS throughout the 6-month period post-CRT (Fig. 2). Its prognostic strength was highest between 3 to 4-months post-CRT, during which the greatest HRs were observed (3 months: HR, 6.06; adj. $p < 0.001$; 95% CI, 2.93 to 12.54; 4 months: HR, 5.40; adj. $p < 0.001$; 95% CI, 2.78 to 10.47). Neutrophil count also showed good prognostic value for OS, with the largest HRs around 4 months. Competing risk analysis for LRPFS and DMFS reported comparatively poorer prognostic value than for OS across all the parameters (S2). Similarly, PLR and its related parameters demonstrated relatively poor prognostic value (S2).

4. Cutoff values

During 3–4 months post-CRT, when the HRs for OS of NLR were the highest, the optimal NLR cutoff ranged from 8.33 to 9.50 (Fig. 3A, 3B). The thresholds for NLR stratified 18 to 19 patients (20.5%–21.3%) above the cutoff and 70 (78.7%–79.5%) below. Bootstrap resampling yielded a median cutoff of 8.14 to 9.35 (3 months: IQR, 7.87 to 9.50; standard error [SE], 2.36; 4 months: IQR, 3.56 to 8.33; SE, 2.55), indicating greater cutoff stability at 3 months post-CRT. For neutrophil count, the most prognostic cutoffs ranged from 7.5 to 7.7 $\times 10^9$/L, with 10 to 12 patients (11.4%–13.5%) above the cutoff and 77 to 78 (86.5%–88.6%) below (Fig. 3C, 3D).

Discussion and Conclusion

In this retrospective study, we aimed to evaluate the prognostic value of measured and calculated hematological parameters related to NLR in stage III unresectable, locally advanced NSCLC treated

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Table 1. Patient and treatment characteristics with univariate analysis and 5-year OS, LRPFS, and DMFS rates

Clinical parameter	No. of patients (%)	5-Year OS (%)	p-value	5-Year LRPFS (%)	p-value	5-Year DMFS (%)	p-value
Age at diagnosis (year)			0.681		0.957		0.910
≤ 65	146 (55.7)	31.3		25.6		22.1	
> 65	116 (44.3)	37.8		29.1		30.4	
Sex			0.005		0.003		0.037
Male	132 (50.4)	28.2		20.1		19.1	
Female	130 (49.6)	40.3		34.4		32.8	
TNM stage			0.043		< 0.001		0.020
IIIA	156 (59.5)	38.4		32.8		29.9	
IIIB	93 (35.5)	31.2		21.7		22.1	
IIIC	13 (5.0)	0		0		0	
ECOG score			0.013		0.052		0.051
0	70 (26.7)	42.5		35.5		31.6	
1	164 (62.6)	33.5		25.9		25.5	
2	25 (9.5)	12.0		12.0		8.0	
3	3 (1.2)	66.7		33.3		66.7	
Smoking history			0.017		0.280		0.351
Yes	247 (94.3)	32.8		26.1		25.4	
No	15 (5.7)	58.7		46.4		33.2	
Histology type			0.662		0.472		0.459
Adenocarcinoma	121 (46.2)	37.4		30.3		25.9	
Squamous cell carcinoma	55 (21.0)	30.6		20.2		25.4	
Other/NOS	86 (32.8)	32.7		30.9		27.2	
Radiation technique			0.995		0.045		0.082
3D-CRT	142 (54.2)	33.3		28.9		26.4	
IMRT	46 (17.6)	30.4		23.8		26.9	
VMAT	74 (28.2)	38.5		26.1		24.2	
Chemotherapy regimen			0.016		0.228		< 0.001
Cisplatin/etoposide	232 (88.5)	33.4		26.7		25.7	
Cisplatin/gemcitabine	1 (0.4)	0		0		0	
Cisplatin/pemetrexed	1 (0.4)	0		0		0	
Carboplatin/paclitaxel	28 (10.7)	42.9		32.1		28.6	
No. of chemotherapy cycles in CRT			0.002		< 0.001		0.004
1	11 (4.2)	18.2		0		10.4	
2	71 (27.1)	27.3		23.6		19.2	
3	29 (11.1)	43.8		36.5		37.0	
4	125 (47.7)	35.7		30.0		28.0	
5	6 (2.3)	66.7		50.0		33.3	
6	15 (5.7)	33.3		13.3		22.9	
7	3 (1.1)	0		0		0	
8	2 (0.8)	100.0		50.0		1.0	

OS, overall survival; LRPFS, locoregional progression–free survival; DMFS, distant metastasi–free survival; ECOG, Eastern Cooperative Oncology Group; NOS, not otherwise specified; 3D-CRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; VMAT, volumetric modulated arc therapy; CRT, chemoradiotherapy.

with concurrent CRT. We analyzed temporal trends to identify time points of potentially heightened prognostic significance and tracked individual cell counts to delineate the relative contributions of neutrophils and lymphocytes. Among all evaluated parameters, post-CRT NLR was the most consistent in demonstrating increased prognostic value in OS (Fig. 2). The association of several NLR-related parameters with OS peaked around 3 to 4 months post-CRT, reflecting time-dependent variation in the prognostic utility of NLR

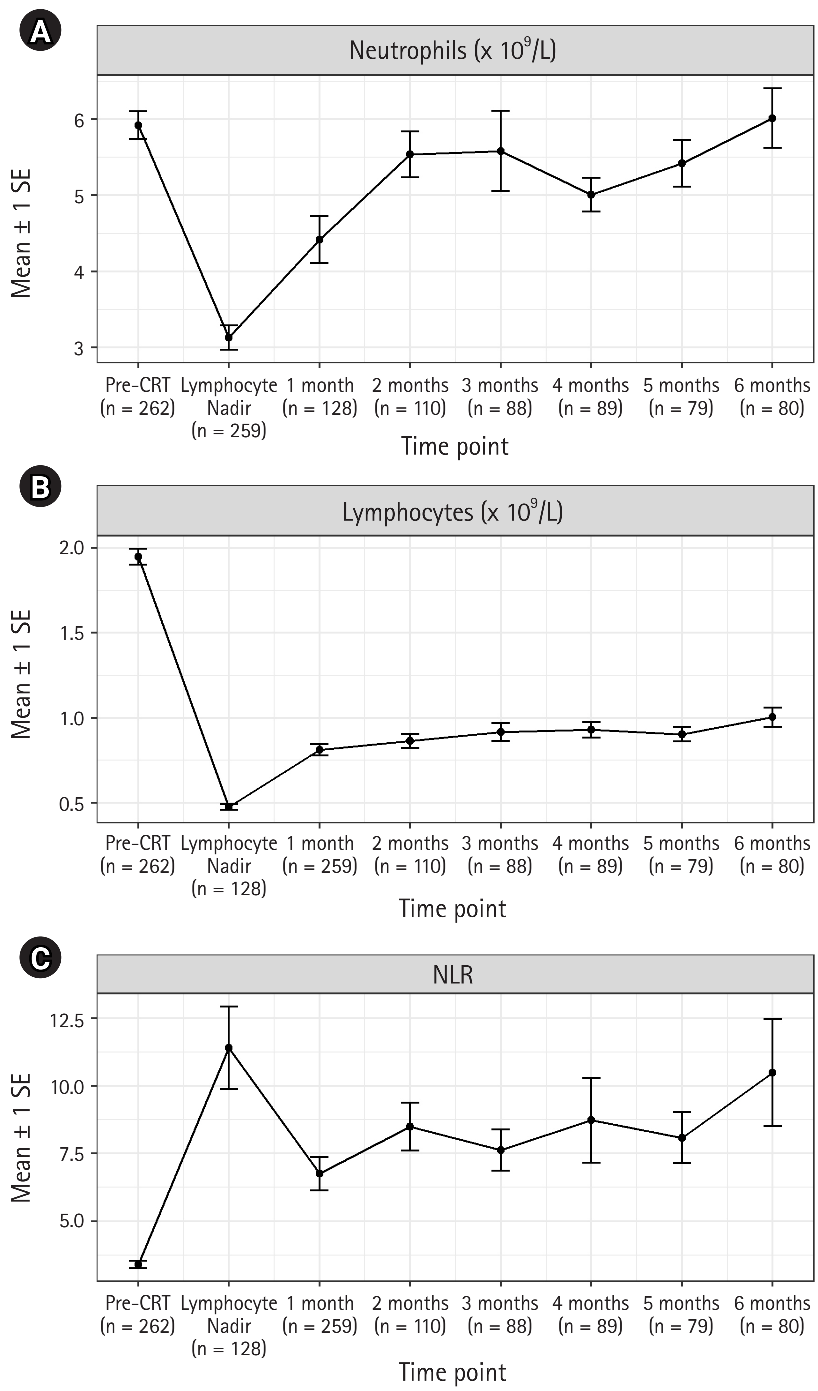

Fig. 1. Measurements of neutrophil count (A), lymphocyte count (B), and neutrophil-to-lymphocyte ratio (NLR) (C) at the pre-chemoradiotherapy (CRT), lymphocyte nadir, and 1 month ± 2-week intervals up to 6 months. Mean NLR increased from pre-CRT to the lymphocyte nadir, driven by a decrease in lymphocyte count, while neutrophil count also decreased by a lesser degree. Mean neutrophil count was also observed to decrease from 3 to 4 months post-CRT.

that may warrant further investigation.

Previous research has generally found NLR to be a significant prognostic marker in this patient population (Table 2). Similar studies focusing on a population with stage III unresectable NSCLC treated with CRT have used comparable pre-CRT measurement timings, but post-CRT timings have varied. Most have used endpoints such as OS and at least one measure of disease progression. To our knowledge, our study is the first to examine NLR at monthly

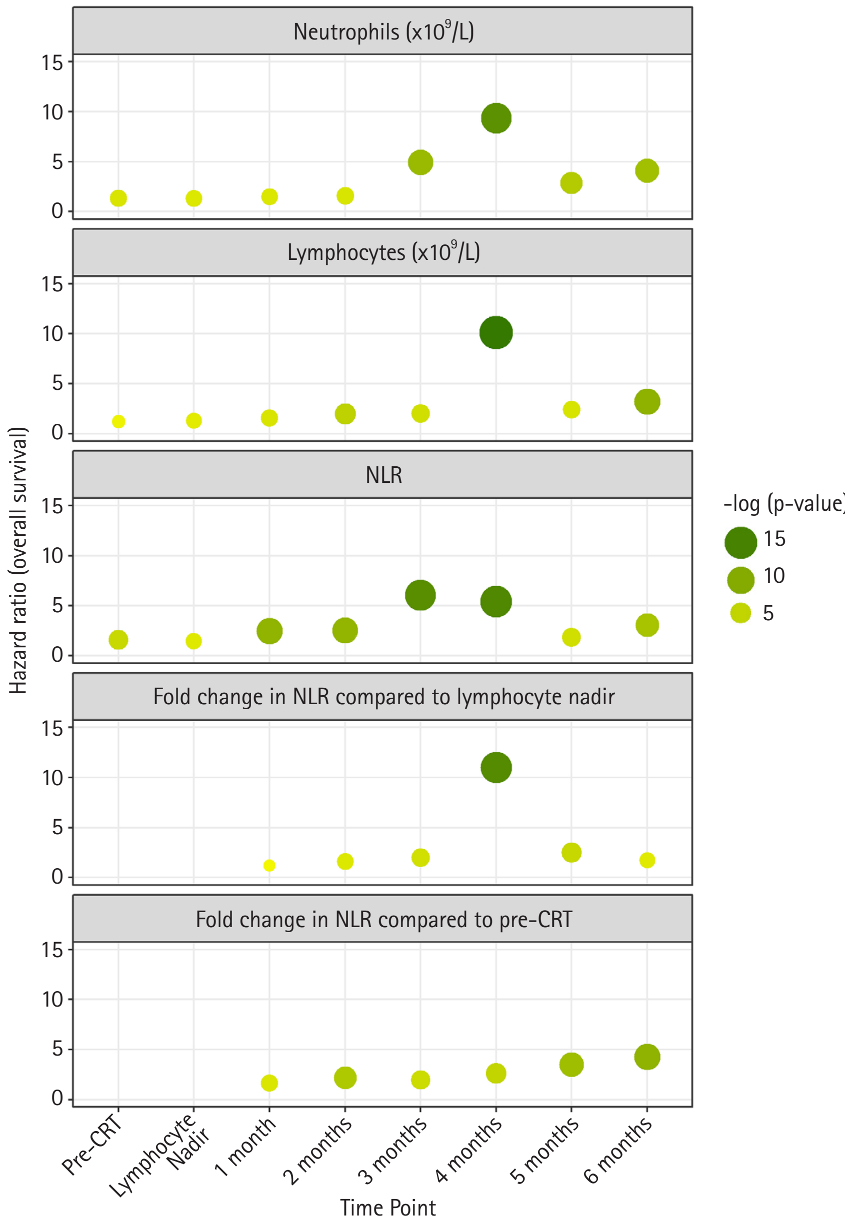

Fig. 2. Hazard ratios of various parameters over time for overall survival. Statistical significance is denoted by colour and size of each point. Post-chemoradiotherapy (CRT) neutrophil-to-lymphocyte ratio (NLR) had the most consistent and robust prognostic value among the parameters explored. NLR at 3–4 months post-CRT, as well as several other parameters, exhibit the greatest prognostic value.

intervals post-CRT. The highest HRs we observed between 3 and 4 months post-CRT (range, 4.0 to 10) were notably higher than those reported in previous studies, which typically ranged from 1.5 to 3.0. Additionally, the NLR cutoffs of prior studies have been generally lower, most commonly ranging from 3 to 7, while our NLR cutoffs at the times with highest prognostic value range from 9.35 to 9.5 (Fig. 3A, 3B). This discrepancy may be due to differences in cutoff determination methods, in which our study used maximum log-rank statistics, whereas others often used either a receiver operating characteristic curve, median/quartiles, or cutoffs from prior literature. Interestingly, at less prognostic time points such as pre-CRT and 5 months post-CRT, our NLR cutoffs (4.73 and 5.2, respectively) were more similar to previous studies. Combined with the higher HRs seen at the 3 to 4-month mark, our findings suggest a potentially underrecognized high-risk subgroup of patients emerging at this time point. Given that these higher-risk individuals constitute a smaller proportion of the population, this may facilitate a more strategic allocation of resources and attention to areas of greatest need. Finally, the variability in NLR cutoff values across studies underscores the challenge of establishing a universal

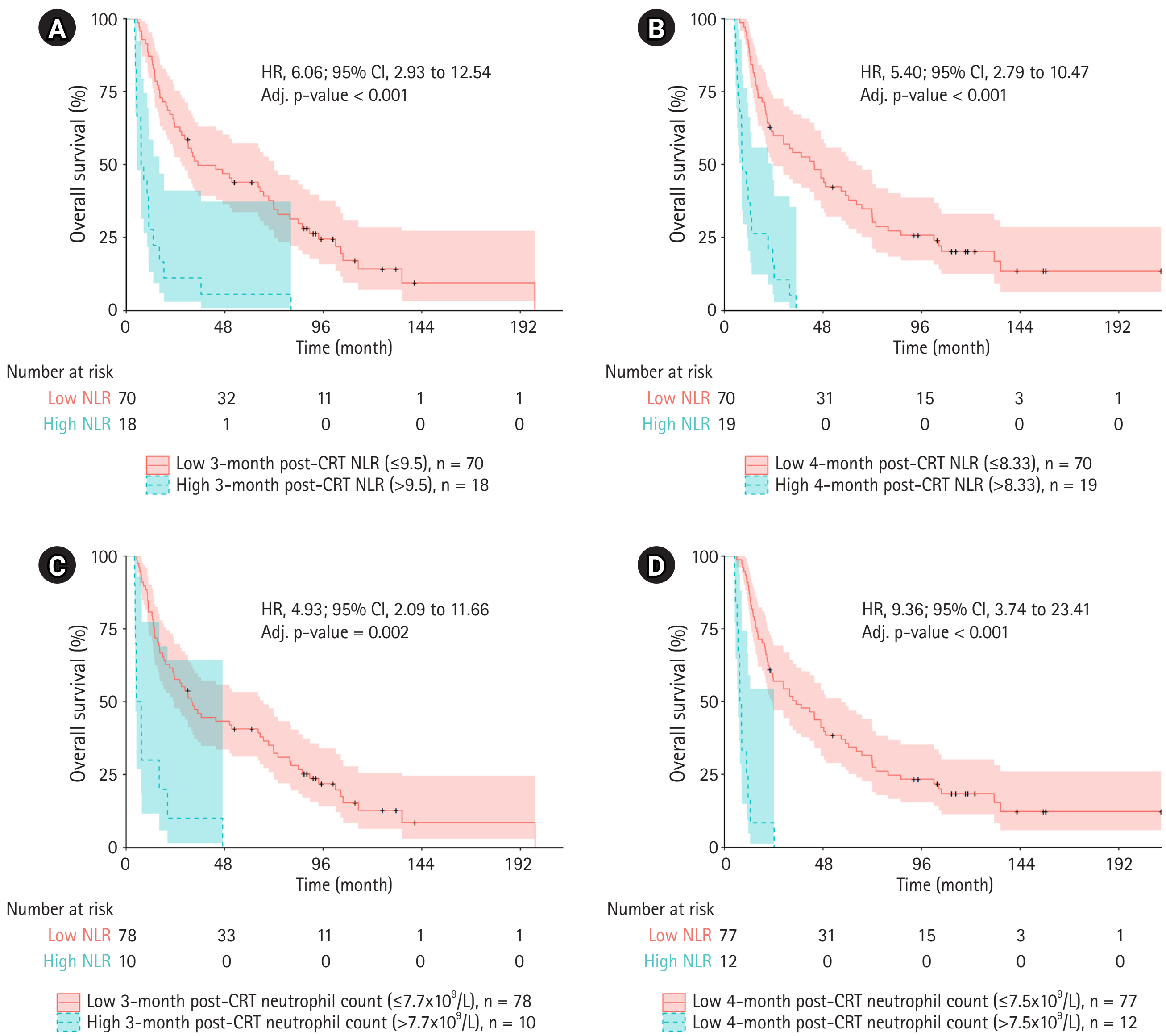

Fig. 3. Kaplan-Meier curves and tables of number at risk for post-chemoradiotherapy (CRT) neutrophil-to-lymphocyte ratio (NLR) (A, B) and neutrophil count (C, D) at the time points with the highest hazard ratios (HRs) for overall survival. Time points were either at 3 months (A, C) or 4 months (B, D). Cutoff values were determined via maximally selected log-rank statistics. Error bars represent 95% confidence interval (CI).

threshold. This heterogeneity likely reflects differences in study design, patient populations, and treatment regimens. As such, prognostic models that integrate NLR alongside other clinical and treatment-related variables may offer greater generalizability and clinical utility than models relying on NLR alone.

Our study uniquely demonstrates that NLR and several related parameters have the greatest prognostic value for OS at specifically 3–4 months post-CRT, a finding not previously reported (Fig. 2). While some prior studies had post-CRT collection periods overlapping with ours, this study offers better temporal resolution that enables more precise comparisons between time points [20,21]. Slightly greater overlap was seen in Contreras et al. [21], in which they examined time points 2- and 4-months post-CRT, though these were defined using broad intervals of 1 to 3- and 3 to 6-months post-CRT, respectively. While they found increased prognostic value at 4 months post-CRT compared to the 2-month time point, they did not compare time points past 4 months, leaving open the possibility that the increased prognostic value could merely be a byproduct of a more accurate reflection of patient recovery as a later time point. Our results showing increased prognostic value of NLR at 3 to 4 months post-CRT compared to both earlier and later time points suggest that there are more nuanced

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Table 2. Summary of studies that have assessed the prognostic value of NLR in stage III unresectable NSCLC treated with CRT without immunotherapy

Study	Study population	Timing of NLR measurement	NLR cutoff value	Endpoints evaluated	Key findings
Sun et al., 2020 [28]	Stage III: unresectable NSCLC; concurrent or sequential CRT; n = 167	1 month pre-CRT	3.06	OS, PFS	High NLR associated with poorer OS (HR, 1.570; p = 0.012) and PFS (HR, 1.471; p = 0.023)
Palomar-Abril et al., 2020 [29]	Stage III: unresectable NSCLC; concurrent or sequential CRT; n = 92	Pre-CRT; 5–6 weeks post-CRT	4 (both)	OS, PFS	High post-CRT NLR associated with poorer OS (HR, 2.81; p < 0.001) and PFS (HR, 2.98; p < 0.001)
Delikgoz Soykut et al., 2022 [14]	Stage III: unresectable NSCLC; concurrent CRT (majority); n = 392	Pre-CRT	3.07	OS, LRPFS, PFS	High NLR associated with poorer OS (HR, 1.73; p < 0.001), LRRFS (HR, 1.76; p < 0.001), and PFS (HR, 1.81; p < 0.001)
Kanzaki et al., 2021 [20]	Stage III: unresectable NSCLC; concurrent CRT; n = 111	2 weeks pre-CRT; 3–4 months post-CRT	4.1; 6.5	OS, LRPFS, DMFS	NLR associated with poorer OS (HR, 1.93; p = 0.028) and DMFS (HR, 1.83; p = 0.040)
Hoffmann et al., 2020 [15]	Stage III: unresectable NSCLC; concurrent or sequential CRT; n = 99	≤ 1 weeks pre-CRT; ≤ 1 weeks post-CRT	3.53	OS	High NLR not significantly associated with poorer OS (HR, 1.52; p = 0.192)
Park et al., 2019 [8]	Stage III: unresectable NSCLC; concurrent CRT; n = 66	≤ 1 weeks pre-CRT; 4 weeks post-CRT	1.64; 3.12	OS, LRPFS, DMFS	High 4 weeks post-CRT NLR not significantly associated with poorer OS (HR, 1.28; p = 0.600) and LRPFS (HR, 0.96; p = 0.919)
Guo et al., 2019 [30]	Stage III: unresectable NSCLC; concurrent CRT; n = 370	Pre-CRT; post-CRT (timing unspecified)	2.94; 2.54	OS, PFS	High post-CRT NLR associated with poorer PFS (HR, 2.575; p = 0.001)
Contreras et al., 2018 [21]	Stage III: unresectable NSCLC; concurrent CRT; n = 127	≤ 2 months pre-CRT; 1–3 months post-CRT; 3–6 months post-CRT	9.5	OS, PFS, LRPFS, DMFS	High NLR at 3–6 months post-CRT associated with poorer OS (HR, 1.02; p < 0.001)
Sebastian et al., 2020 [31]	Stage III: unresectable NSCLC; concurrent CRT; n = 135	1-2 weeks pre-CRT; 1-month post-CRT; 3 months post-CRT	5; 6.3; 6.6	OS, PFS, LRPFS, DMFS	High pre-CRT NLR associated with poorer OS (HR, 1.82; p = 0.011). High NLR at 3 months post-CRT associated with poorer OS (HR, 1.06; p < 0.001), PFS (HR, 1.10; p < 0.001), LRPFS (HR, 1.07; p < 0.001), and DMFS (HR, 1.09; p < 0.001)
Our study	Stage III: unresectable NSCLC; concurrent CRT; n = 262	Pre-CRT; lymphocyte nadir; 1 month ± 2-week intervals up to 6 months post-CRT	Varied based on time point and endpoint	OS, LRPFS, DMFS	High NLR at 3–4 months post-CRT is the most prognostic period for poor prognosis

NLR, neutrophil-to-lymphocyte ratio; NSCLC, non–small cell lung cancer; CRT, chemoradiotherapy; OS, overall survival; PFS, progression-free survival; HR, hazard ratio; LRPFS, locoregional progression–free survival; DMFS, distant metastasis–free survival.

temporal dynamics in the relationship between systemic inflammation and survival.

Recent studies that have examined NLR (or derived NLR) as a prognostic marker in NSCLC in the context of consolidation immunotherapy have generally reported high NLR to be predictive for poor outcomes [22-26]. These studies included at least one NLR measurement after concurrent chemoradiation and before treatment with durvalumab, using NLR cutoffs at or around 3. However, the timings of the measurements for NLR led to some varied results. Interestingly, several studies found that the pre-immunotherapy NLR alone had relatively poor prognostic value [22,24,25,27]. Parameters that were better for prognostication included pre-CRT NLR, NLR after the start of immunotherapy, or rising and sustained NLR elevation [22,24,25]. The poor prognostic value of NLR immediately following CRT but prior to immunotherapy may be a product of the immunosuppressive effects of CRT and possible interactions with immunotherapy. Notably, Sugimoto et al. [24] found that high pre-durvalumab NLR was predictive for immune-related adverse events and check-point inhibitor-related pneumonitis, further suggesting potential interactions between NLR and immunotherapy. While it is difficult to directly compare our findings to these studies, differences in the prognostic value of NLR at different time points also demonstrate that NLR measurement timing may be important for prognostication, even in the more modern era of routine immunotherapy use.

The mechanisms underlying the increased prognostic value of individual cell counts, NLR, and fold change of NLR (relative to the lymphocyte nadir) around 3 to 4 months post-CRT remain unclear. Nonetheless, these results indicate that the current standard for post-treatment bloodwork, which varies by region, may benefit from greater standardization that includes routine bloodwork at 3–4 months post-CRT. Since the introduction of durvalumab consolidation therapy for locally advanced NSCLC, regular bloodwork every 2–4 weeks has become more common [4]. As such, increasing post-CRT bloodwork frequency may be more applicable for patients not receiving durvalumab. With respect to approaches for escalation in disease surveillance and treatment in response to higher mortality risk, increased surveillance imaging for recurrence can be considered. Current guidelines by the American Society of Clinical Oncology recommend diagnostic chest computed tomography (CT) scans every 6 months for 2 years to monitor for recurrence [32]. However, these recommendations primarily focus on patients with earlier stage, resected NSCLC. The National Comprehensive Cancer Network guidelines outline similar recommendations, with surveillance after post-CRT beginning with a chest CT (with or without contrast) every 3–6 months for 3 years [33]. This broader range allows clinicians to tailor surveillance intensity based on patient-specific factors, potentially providing an opportunity for further risk stratification to guide management. Overall, there may be areas in current practice and guidelines that can be improved in terms of identifying higher risk groups, especially within patients diagnosed with unresectable, locally advanced NSCLC for consideration for more intensive surveillance.

Increased post-CRT NLR and neutrophil count were consistently associated with poorer prognosis (Figs. 2, 3). The prognostic utility of NLR is thought to stem from the biological roles of its components, neutrophils and lymphocytes, in tumour-mediated systemic inflammation and the host response to RT toxicity [10,11]. Neutrophilia is a well-recognized phenomenon in cancer, driving multiple mechanisms that promote tumor progression, including enhanced angiogenesis, inhibition of apoptosis, cytokine-mediated invasion, and increased oxidative stress [10,34]. Additionally, tumour-associated neutrophils (TANs) have been observed to exhibit two distinct phenotypes, the anti-tumorigenic N1 and the pro-tumorigenic N2 subtypes [35]. TANs tend to exhibit an N1 phenotype during early tumor development, while shifting toward a more pro-tumorigenic N2 phenotype in later stages [36]. Although our study did not evaluate TAN phenotypes directly, the expected predominance of N2 TANs in later-stage NSCLC may also contribute to the observed association between elevated neutrophil counts and poorer prognosis. Overall, various neutrophil-mediated mechanisms may underlie the adverse prognosis associated with neutrophilia in cancer. In contrast, PLR and its related parameters had relatively low HRs compared to NLR. Consistent with prior research demonstrating the superior prognostic value of NLR, our results suggest that PLR lacks a strong basis to be further pursued as a prognostic marker at the time points assessed in our study (S2) [8,14,15].

Radiation-induced lymphopenia (RIL) is another well-established adverse prognostic factor in lung cancer, and has been identified as a key contributor to differences in OS [37-39]. Platinum-based chemotherapeutic agents, commonly used in CRT for stage III NSCLC, also contribute to lymphopenia [40,41]. In concordance with these phenomena, we observed that increases in NLR were largely driven by declines in lymphocyte count, particularly the changes from pre-CRT values to the lymphocyte nadir and subsequent time points. These changes in NLR were dampened by decreases in neutrophil count, in which neutropenia is a known side effect of CRT [42]. The proportionally greater decrease in lymphocyte count is congruent with past studies demonstrating that lymphocytes are more sensitive to chemoradiation than neutrophils [9]. While lymphocyte count remained relatively stable at later time points, neutrophil counts demonstrated greater fluctuation, likely reflecting the longer lifespan and slower turnover of lymphocytes [43].

Our study has several limitations. As the study is retrospective in nature, there were no standardized protocols for key aspects such as the timing of blood draws, treatment selection, and follow-up intensity. This introduces potential heterogeneity in data collection and treatment exposure that could affect the results. In particular, regarding hematologic parameters collected between 3–6 months post-CRT, laboratory assessments may have been performed based on clinical symptoms or disease progression rather than routine surveillance. This may lead to confounding by indication, where elevated NLR may reflect symptomatic progression rather than being an independent prognostic marker. Our data also does not include potential confounders such as programmed death-ligand 1 (PD-L1) status and epidermal growth factor receptor (EGFR) positivity, in which BC Cancer did not adopt molecular testing for EGFR until 2010 and PD-L1 until 2017. Additionally, interpretation of statistical significance is complicated by multiple testing across different time points, each with varying sample sizes, with later time points having less available data than earlier ones. The small subgroups stratified by our cutoffs may also have potentially conflated the HRs from Cox regression analysis of OS. As this was a single-institution study, we did not have other data sets available for external validation, which limits the generalizability of our findings. Lastly, we recognize that biomarkers examined at earlier time points, especially before treatment, are generally more useful for clinical decision-making and prognostication than later ones. Although our data at earlier time points yielded results consistent with previous studies, the novelty of our work lies in demonstrating increased prognostic value within a specific later time window, which was the focus of our study.

Directions for future studies include investigating the relationship between RT dose to immune-related organs-at-risk (OARs) and hematologic parameters, including NLR and cell counts. Prior research has shown that post-CRT lymphopenia is correlated with the effective dose to immune cells [44]. Immune-relevant OARs in the context of thoracic RT, including the heart, great vessels, and

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lungs have been implicated in RIL. A promising approach to quantify this relationship is the Hematological Dose (HEDOS) framework, which integrates treatment geometry, temporal dose delivery, and modeled blood particle distribution to estimate RT dose delivered to circulating immune cells [45]. Incorporating HEDOS would not only enhance the mechanistic plausibility of NLR dynamics post-CRT but also support research into treatment planning strategies that minimize hematological toxicity. Additionally, the use of durvalumab and its efficacy may be negatively affected by RIL, which introduces another layer of complexity that should be explored in future studies that include immunotherapy [4,46]. Finally, machine learning approaches could be used to build prognostic models incorporating a wide range of clinical, laboratory, and dosimetric data to facilitate personalized treatment strategies and improve prognostic accuracy.

Our study evaluated the prognostic value of NLR at multiple time points, including pre-CRT, lymphocyte nadir, and each month post-CRT up to 6 months in patients with stage III unresectable, locally advanced NSCLC treated with concurrent CRT. By analyzing longitudinal trends in neutrophil and lymphocyte counts, we found that NLR at the 3 to 4-month mark post-CRT demonstrated increased prognostic value for OS. This time window represents a potential opportunity for future investigation into the variation of the prognostic value of NLR over time.

Statement of Ethics

This study was approved by the BC Cancer Research Ethics Board (H23-02261). Patient consent for this retrospective chart review was waived by the BC Cancer Research Ethics Board. No identifying patient information is included in this article.

Conflict of Interest

YHX and LTH no conflicts of interest. JSC owns stock in Oncosoft. SR has received honoraria/payment from AstraZeneca, Pfizer, and Bristol-Myers Squibb. AS received a stipend from the University of British Columbia Faculty of Medicine Summer Student Research Program. SA is a Canadian Association of Radiation Oncology Board Member.

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Author Contributions

Conceptualization, YHX, LTH, JSC, SR, AS, SA; Study design, YHX, LTH, JSC, SR, AS, SA; Data analysis and visualization, YHX; Writing of the original draft, YHX, LTH; Writing of the review and editing, YHX, LTH, JSC, SR, SA.

Data Availability Statement

The data that support the findings of this study are not publicly available due to inclusion of patient data but can be requested from BC Cancer (reb@bccancer.bc.ca).

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