Neutrophil-lymphocyte ratio & absolute lymphocyte count as prognostic markers in patients treated with curative intent radiotherapy for NSCLC.

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Abstract:

Introduction: Neutrophil-Lymphocyte ratio (NLR) and absolute lymphocyte count (ALC) have been proposed as prognostic markers non-small cell lung cancer (NSCLC). The objective of this study was to examine the association of NLR/ALC pre and post curative-intent radiotherapy (RT) for NSCLC on disease recurrence and overall survival.

Methods: A retrospective study of consecutive patients who underwent curative-intent RT for NSCLC across 9 sites in the UK from 01/10/2014 to 01/10/2016. A multivariate analysis of the ability of pre-treatment NLR/ALC, post-treatment NLR/ALC and change in NLR/ALC, adjusted for co-founding factors using the Cox proportional hazards model, to predict disease recurrence and overall survival (OS) within 2 years of treatment.

Results: 425 patients were identified with complete blood parameter values. Higher pre-NLR, post-NLR and change in NLR plus lower post ALC were all independent predictors of worse survival. Receiver operator curve analysis found pre-NLR >2.5 (OR 1.71, 95%CI 1.06-2.79, p< 0.05), post-NLR >5.5 (OR 2.36, 95%CI 1.49-3.76, p< 0.001], change in NLR >3.6 (OR 2.41, 95%CI 1.5-3.91, p<0.001) and post ALC <0.8 (OR 2.86, 95%CI 1.76-4.69, p <0.001) optimally predicted poor overall survival on both univariate and multivariate analysis when adjusted for cofounding factors. None of the NLR/ALC parameters were independent predictors of disease recurrence.

Conclusion: NLR and ALC, surrogate markers for systemic inflammation, have prognostic value in NSCLC patients treated with curative intent radiotherapy. These simple and readily available parameters may have a future role in risk stratification post treatment to inform the intensity of surveillance protocols.

Introduction

There is an increasing body of research demonstrating that inflammation in the solid tumour microenvironment promotes proliferation, survival and migration of the neoplastic process (1). Peripheral circulatory blood cells like neutrophils and lymphocytes can be used as surrogate markers which reflect the equilibrium between pro and anti-inflammatory cytokines in the tumour microenvironment. Neutrophils promote tumourogenesis by various mechanisms. They secrete pro-angiogenic factors thus fostering angiogenesis, release various growth factors from proteolysis of extracellular matrix and recruit other tumour promoting cells (2,3). Lymphocytes on the other hand promote anti-tumour immunity by stimulating apoptosis and suppressing the proliferation and migration of tumour cells (4-6). Neutrophil-lymphocyte ratio (NLR) is defined as the absolute neutrophil count / absolute Lymphocyte count. It reflects the balance between the opposing inflammatory pathways with any escalation of neutrophilic actions and/or decline in lymphocytic action leading to a state of pro-inflammation and tumourogenesis. This systemic inflammation ratio has been studied in different solid cancers including lung cancer and has been found to have prognostic significance in various meta-analyses (7-11).

Different modalities of radiotherapy (RT) are used in modern day thoracic oncology for the curative-intent treatment of non-small cell lung cancer (NSCLC). Radiotherapy itself acts as a double edged sword on the immune system by having both immunostimulatory and immunosuppressive effects. Various studies have looked at either the pre-treatment or the post-treatment NLR and absolute lymphocyte count (ALC) values individually in patients treated with a single modality of RT. However no studies have examined the breath of these values across differing radiotherapy modalities at both time points and, therefore, have also

not explored the impact of dynamic changes in systemic inflammation over the RT treatment period on prognosis and disease recurrence in NSCLC. The objective of this study was to examine the pre-treatment, post-treatment and dynamic change in NLR and ALC in patients with NSCLC treated with curative intent RT.

Methods:

Retrospective data was collected for consecutive patients that underwent curative-intent radiotherapy for NSCLC from 1st October 2014 to 1st October 2016 at nine trusts across the United Kingdom (Wythenshawe Hospital, The Christie NHS Foundation Trust, Royal Marsden Hospital, University College London Hospitals, Papworth Hospital NHS Foundation Trust, Addenbrookes Hospital, Sheffield Teaching Hospitals Trust, NHS Greater Glasgow and Clyde Trust and Queen Elizabeth Hospital Belfast). The data was collected in early 2019 ensuring a minimum of two years follow-up data for all patients and the database locked in April 2019 for analysis. The data was retrieved from case note and electronic patient record review. The following demographic, clinical and treatment-related parameters were collected: age, gender, pre-treatment performance status, overall clinical stage (8th edition TNM), smoking status, pathological diagnosis of NSCLC (yes/no), histological sub-typing of NSCLC (squamous cell carcinoma, adenocarcinoma, NSCLC-NOS), emphysema (reported on CT scan yes/no), interstitial lung disease (reported on CT scan yes/no), type of radiotherapy treatment used (Conventional radical radiotherapy, stereotactic ablative radiotherapy (SABR), sequential chemoradiotherapy, concurrent chemoradiotherapy or continuous hyper-fractionated accelerated radiotherapy (CHART)), pre & post-treatment neutrophil-lymphocyte ratio and pre & post-treatment absolute lymphocyte count. In addition, the following outcome data was collected: disease status (disease free versus disease recurrence), date of disease recurrence, survival status (alive/died) and date of death.

The primary objective of this study was to look at pre-treatment, post-treatment and change in NLR and ALC values and see if there was any independent correlation of these parameters with disease recurrence and death within two years of follow up. The pre-treatment value was defined as the blood test performed closest to the start date of RT but was no longer than 6 weeks prior this start date. The post-treatment value was defined as the blood test performed closest to but not beyond 4 weeks after the completion date of RT. The centres contributing to this dataset are mostly tertiary radiotherapy centres that receive referrals on a regional footprint. In this retrospective study we anticipated challenges in missing data fields, particularly where blood tests were performed at separate hospitals to where the radiotherapy was completed. This informed the decision to recruit a high number of centres for this study and include consecutive patients from a two-year study period. The study cohort would then be restricted to those with a complete set of NLR/ALC results. From this cohort those patients with complete outcome data would be used in the statistical analysis.

Statistical Analysis. The statistical analysis was done using SPSS version R version 4.0.1, with a threshold of <0.05 to determine statistical significance. Optimal cut-off points for the prediction of disease recurrence and death with pre-treatment, post-treatment and change (Δ) in NLR and ALC were calculated by maximising the Youden index. These optimal cut-off points were then examined in regression analyses, adjusting for cofounders with univariable significance <0.1. Potential confounding prognostic factors that were included in the analysis were: age, sex, performance status, smoking history, history of interstitial lung disease (ILD), emphysema, stage of lung cancer, type of radiotherapy and pathological sub-type of NSCLC. The Kaplan-Meier method was used to analyse time-to-event outcomes, with log-rank tests to compare survival distributions for those variables found to be significant predictors of

outcome after adjustment for cofounding factors. Ethical approval was not required given the observational nature of the study, confirmed via discussion with the local ethics committee.

Results:

A total of 898 patients underwent curative intent radiotherapy for NSCLC in the study period across the nine centres. Complete data for all blood parameters were recorded in 47% (425/898) for whom a summary of patient characteristics is provided in Table 1. Median age was 71 years and 52% (221/425) were males. 56% (236/425) had a pre-treatment performance status 0-1. 31% (131/425) were clinical TNM stage I and 55% (233/425) were stage III. 28% (119/425) were current smokers. A pathological diagnosis of NSCLC was achieved in 79% (337/425) with the commonest histological sub-type being squamous cell carcinoma in 29% (122/425). 31% (131/425) and 8% (30/425) had a radiological diagnosis of emphysema and ILD respectively. The commonest type of radiotherapy given was conventional radiotherapy in 41% (174/425) of cases. The median values for the blood parameters were pre-NLR 3, post-NLR 5.9, change in NLR 4.5, pre-ALC 1.6, post-ALC 0.8 and change in ALC -0.9.

Complete outcome data for disease recurrence was available for 90% (382/425) of patients (Figure 1). 43% (163/382) of patients suffered disease recurrence within 2 years of curative intent RT. 30% (48/163) were detected due to symptomatic presentation and 70% (115/163)

were detected through routine surveillance imaging in the absence of symptoms. The pattern of disease recurrence was as follows: local recurrence in 27% (44/163), nodal recurrence in 8% (13/163) and distant recurrence in 65% (106/163). Patients with disease recurrence underwent the following treatment: surgical resection 1% (2/163), radical radiotherapy for nodal/local recurrence 5% (9/163) and palliative systemic anti-cancer treatment 35% (58/163). The common management strategy for disease recurrence was best supportive care (59%, 94/163).

Complete outcome data for survival was available for 89% (379/425) of patients (Figure 1). 45% (170/379) of patients died within 2 years of curative intent RT. The cause of death was recorded as follows; lung cancer-related death 58% (99/170), non-cancer related death 25% (43/170), treatment related death in 4% (7/170) and unknown in 12% (21/170).

NLR/ALC and disease recurrence. Optimal cut-off points for the prediction of disease recurrence within two years were calculated for Pre-NLR (>2.8), post-NLR (>4.7), Δ-NLR (>5.9), pre-ALC (>1.8), post-ALC (≤0.9) and Δ-ALC (>0.65). Only post-ALC (<0.9) and Δ-ALC (>-0.65) were associated with a statistically significant increase in the risk of disease recurrence (post-ALC OR 1.52, 95%CI 0.82-2.83, p<0.001 and Δ-ALC OR 0.58, 95%CI 0.32-1.03, p=0.02) on univariate analysis. However there was no statistically significant increase in the risk of disease recurrence in any of the values after adjusting for confounding factors, especially with univariable significance <0.1 namely: age, performance status, overall stage, pathological diagnosis, NSCLC sub-type and radiotherapy modality used (Tables 2 & 3).

NLR/ALC and survival. Optimal cut-off points for the prediction of death within two years were calculated for Pre-NLR (>2.5), post-NLR (>5.5), Δ-NLR (>3.6), pre-ALC (>2.2), post-ALC (≤0.8) and Δ-ALC (≤-0.9). Pre-NLR >2.5 (OR 1.71, 95%CI 1.06-2.79, p<0.05), post-NLR >5.5 (OR 2.36 95%CI 1.49-3.76, p<0.001), Δ-NLR >3.6 (OR 2.41 95%CI 1.5-3.91, p<0.001) and post-ALC

<0.8 (OR 2.86, 95%CI 1.76-4.69, p<0.001) were statistically significant independent predictors of death within 2 years on univariate and multivariate analysis when adjusted for cofounding factors (Tables 4 & 5). The median overall survival for the high-risk group versus low-risk group for pre-NLR, post-NLR, Δ-NLR and post-ALC were: 770 versus 1009 days (p=0.34), 596 versus 1287 days (p=<0.001), 553 versus 1214 days (p=<0.001) and 594 versus 1287 days respectively (Figure 2).

Discussion:

Key findings. This multicentre study across nine hospitals trusts in the UK has examined the correlation of peripheral blood inflammatory markers (NLR & ALC) and disease recurrence and overall survival in NSCLC patients undergoing curative intent RT. There no association between any peripheral blood markers and disease recurrence once adjusted for cofounding variables. High NLR values both pre (>2.5) and post (>5.5) treatment, the change in NLR (>3.6) and post-treatment ALC (≤0.8) were all independent predictors of death within 2yrs of completing RT when adjusted for cofounding factors. Post Treatment NLR >5.5, a change in NLR of >3.6 from pre-post treatment and post treatment ALC <0.8 were associated with a significantly reduced median overall survival from >1200 days to approximately 500-600 days.

Context with published literature. In a study done by Sebastain et al, pre -treatment NLR >3.6 predicted poor OS in patients with early stage NSCLC treated with SABR (16).This is similar to

the findings in our study though the optimal pre-NLR cut-off was lower in our study. Wang et al found significant correlation with higher ΔNLR and post-NLR values and poor OS in patients treated with concurrent radiotherapy for stage 3 lung cancer (19). A meta-analysis done by Zhou et al which included more than 7,000 patients in 22 studies also reported high NLR as an independent predictor of poor OS in lung cancer. The analysis included patients in different stages with NLR cut -off values ranging between 2-5 (17). These findings have been replicated in other meta-analysis as well (18, 20). In our study we didn't find any significant correlation between pre-treatment ALC and survival outcomes. This is in keeping with a meta-analysis done by Zhou et al which found no significant correlation with pre-ALC and OS in 5 studies of lung cancer with over 1300 patients[H.R -1.2(C.I-0.92-1.57), p value-0.177](21). Furthermore, our study identified low post-ALC was an independent predictor of poor OS. Tang et al reported similar findings in a large dataset of >700 NSCLC treated with RT with lower ALC values post treatment predicting poor OS (22). Other studies done by Campian et all and Joo et al have also shown similar findings (23,24). One possible reason could be post radiotherapy related lymphopenia which tips the balance in favour of pro inflammatory microenvironment which promotes tumour growth as well as increased incidence of infections. Further studies are needed to clarify the effect of potential influencing factors such as irradiated blood volume and choice of therapy on circulating lymphocytes.

Strengths of our study. This is a large multicentre study looking at different stages and different modalities of radiotherapy treatment in NSCLC patients and across stages I-III. This makes the findings of the study applicable to a broad range of lung cancer patients. Also this study looked at dynamic change in inflammatory variables as opposed to a single value which better reflects the change in tumour microenvironment during treatment. A further strength

is the adjustment for cofounding variables and the depth of data collected to undertake this adjustment.

Weaknesses of the study. This is a retrospective study and was therefore reliant upon the availability of the relevant data. 53% of patients within the study period did not have the required blood parameters to be included in the final analysis. This suggests a number of weaknesses to this study. Firstly, although these routine blood tests are readily available, our study suggests it is not currently routine practice to measure these parameters within treatment centres in the required time periods pre and post treatment. This may question how translatable the findings are into routine practice, particularly with the transfer of care between referring and treatment centres. Secondly, the selection of only those with the required blood test results may introduce a bias of patient selection that influences the findings of the study. Finally, the retrospective nature of this study also means there was no standardisation of the timing of blood sampling. To ensure the maximal inclusion of patients there were relatively broad inclusion criteria of within 6 weeks of starting treatment and within 4 weeks of finishing treatment. Peripheral blood cell levels will be subject to variability and the potential inconsistency of timing of the pre and post levels may influence the findings. There are no universally accepted optimal cut-off values for these peripheral blood parameters with differing values used within differing studies. This makes it difficult to use it as a biomarker predictor in risk stratified models. Finally, NLR values can be affected by other confounding factors like infections, sepsis and steroid use which would not be accounted for in this study.

Conclusion. Our study has shown a strong association of post treatment NLR and ALC values, as well as the change in NLR from pre to post treatment, as independent predictors of poor overall survival in NSCLC patients treated with different curative RT in different stages. These

prognostic markers could have applicability in risk stratified follow-up protocols by identifying patients at higher risk of death warranting a more intensive surveillance protocol.

Table 1: Patient demographic and clinical parameters

Variable		n=425
Age (mean)		71
Gender n (%)	Male	221 (52)
	Female	204 (48)
Performance status n (%)	0	51 (10)
	1	185 (44)
	2	147 (35)
	3	31 (7)
	Missing	11 (3)
Overall stage n (%)	I	131 (31)
	II	61 (14)
	III	233 (55)

	Missing	0 (0)
Smoking n (%)	Never	22 (5)
	Current	119 (28)
	Ex-smoker	263 (62)
	Missing	21 (5)
Pathological diagnosis n (%)	Yes	337 (79)
	No	88 (21)
	Missing	0 (0)
Histological sub-type n (%)	SqCC	122 (29)
	Adenocarcinoma	117 (28)
	NSCLC-NOS	98 (23)
	Missing	(0)
Emphysema n (%)	Yes	131 (31)
	No	202 (48)
	Missing	92 (22)
Interstitial Lung disease n (%)	Yes	35 (8)
	No	296 (70)
	Missing	94 (22)
Type of radiotherapy n (%)	Conventional	174 (41)
	SABR	73 (17)
	sCRT	102 (24)
	cCRT	55 (13)
	CHART	21 (5)
	Missing	0 (0)
NLR (median)	Pre-NLR	3
	Post-NLR	5.9
	Δ-NLR	4.5
ALC (median)	Pre treatment	1.6
	Post treatment	0.8
	Δ ALC	-0.9

**SqCC: Squamous cell carcinoma, Non-small cell lung cancer-not otherwise specified, SABR; Stereotactic ablative radiotherapy, sCRT: sequential chemoradiotherapy, cCRT: concurrent chemoradiotherapy, CHART: continuous hyperfractionated accelerated radiotherapy*

Table 2: Baseline characteristics and univariate logistic regression for the outcome of recurrence within 2 years (n=382)

Cofounding factors		**No recurrence N=219**	**Recurrence N=163**	**OR (95% CI)**	**P-value**
Age Mean (IQR)		74 (44-96)	70 (35-96)	0.95 (0.93-0.97)	<0.001
Performance Status n (%)	0	19 (9)	32 (20)	1	
	1	101 (46)	82 (50)	0.48 (0.25-0.9)	0.02
	2	79 (36)	42 (26)	0.32 (0.16-0.62)	<0.001
	3	15 (7)	4 (3)	0.16 (0.04-0.51)	0.004
	Missing	5 (2)	3 (2)		
Overall Stage TNM 8th Edition n (%)	I	93 (42)	33 (20)	1	
	II	32 (15)	20 (12)	1.74 (0.87-3.45)	0.11
	III	94 (43)	110 (68)	3.26 (2.03-5.34)	<0.001
	Missing	0 (0)	0 (0)		
Smoking status	Never	13 (6)	7 (4)	1	
	Ex-smoker	131 (60)	99 (61)	1.4 (0.55-3.86)	0.49

n (%)	Current	62 (28)	49 (30)	1.47 (0.56-4.17)	0.45
	Missing	13 (6)	8 (5)		
Pathological diagnosis n (%)	No	58 (27)	23 (14)	1	
	Yes	161 (73)	140 (86)	2.19 (1.3-3.8)	0.004
	Missing	0 (0)	0 (0)		
Histological subtyping n (%)	No diagnosis	58 (27)	23 (14)	1	
	SqCC	59 (27)	48 (29)	2.05 (1.12-3.84)	0.02
	Adenocarcinoma	64 (29)	39 (24)	1.54 (0.83-2.9)	0.18
	NSCLC-NOS	38 (17)	53 (33)	3.52 (1.88-6.75)	0.001
	Missing	0 (0)	0 (0)		
Emphysema n (%)	No	109 (50)	72 (44)	1	
	Yes	73 (33)	43 (26)	0.89 (0.55-1.44)	0.64
	Missing	37 (17)	48 (29)		
Interstitial lung disease n (%)	No	161 (74)	104 (64)	1	
	Yes	21 (10)	11 (7)	0.81 (0.36-1.72)	0.59
	Missing	37 (17)	48 (29)		
Type of radiotherapy n (%)	Conventional	93 (42)	58 (36)	1	
	SABR	55 (25)	16 (10)	0.47 (0.24-0.88)	0.02
	sCRT	36 (16)	56 (34)	2.49 (1.47-4.27)	<0.001
	cCRT	20 (9)	28 (17)	2.24 (1.17-4.39)	0.02
	CHART	15 (7)	5 (30	0.53 (0.17-1.46)	0.25
	Missing	0 (0)	0 (0)		

**SqCC: Squamous cell carcinoma, Non-small cell lung cancer-not otherwise specified, SABR; Stereotactic ablative radiotherapy, sCRT: sequential chemoradiotherapy, cCRT: concurrent chemoradiotherapy, CHART: continuous hyperfractionated accelerated radiotherapy*

Table 3: Univariate and multivariate analysis for NLR/ALC and disease recurrence.

Variable		Unadjusted OR (95% CI)	p-value	Adjusted OR* (95% CI)	p-value
Pre-treatment NLR	≤2.8	1		1	
	>2.8	1.05 (0.7-1.58)	0.81	1.37 (0.87-2.18)	0.18
Post-treatment NLR	≤4.7	1		1	
	>4.7	1.19 (0.79-1.81)	0.4	1.1 (0.69-1.74)	0.69
Change in NLR	≤5.9	1		1	

	>5.9	0.99 (0.61-1.6)	0.96	0.79 (0.46-1.35)	0.39
Pre-treatment ALC	≤1.8	1		1	
	>1.8	1.13 (0.74-1.71)	0.57	1.03 (0.65-1.62)	0.91
Post-treatment ALC	>0.9	1		1	
	≤0.9	1.78 (1.16-2.74)	0.009	1.38 (0.85-2.26)	0.19
Change in ALC	≤-0.65	1		1	
	>-0.65	0.61 (0.4-0.93)	0.02	0.82 (0.51-1.32)	0.41

**Adjusting for cofounders with univariate significance <0.1 (age, PS, stage, histological sub-type & type of radiotherapy)*
***NLR: Neutrophil-lymphocyte ratio, ALC: Absolute lymphocyte count*

Table 4: Baseline characteristics and univariate logistic regression for the outcome of death within 2 years (n=379)

Cofounding factors		**Alive N=209**	**died N=170**	**OR (95% CI)**	**P-value**
Age Mean (IQR)		71 (44-89)	72 (35-96)	1.01 (0.98-1.03)	0.55
Performance Status n (%)	0	29 (14)	21 (12)	1	
	1	100 (48)	85 (50)	1.17 (0.63-2.23)	0.62
	2	64 (31)	53 (31)	1.14 (0.59-2.25)	0.69
	3	11 (5)	8 (5)	1 (0.34-2.92)	0.99
	Missing	5 (2)	3 (2)		
Overall Stage TNM 8th Edition n (%)	I	86 (41)	36 (21)	1	
	II	33 (16)	21 (12)	1.5 (0.76-2.94)	0.24
	III	90 (43)	113 (67)	2.96 (1.85-4.82)	<0.001

	Missing	0 (0)	0 (0)		
Smoking status n (%)	Never	16 (8)	4 (2)	1	
	Ex-smoker	117 (56)	112 (66)	3.83 (1.36-13.68)	0.02
	Current	61 (29)	48 (28)	3.15 (1.07-11.54)	0.05
	Missing	15 (7)	6 (4)		
Pathological diagnosis n (%)	No	62 (30)	20 (12)	1	
	Yes	147 (70)	150 (88)	3.16 (1.85-5.61)	<0.001
	Missing	0 (0)	0 (0)		
Histological subtyping n (%)	No diagnosis	62 (30)	20 (12)	1	
	SqCC	39 (19)	61 (36)	4.85 (2.58-9.4)	<0.001
	Adenocarcinoma	58 (28)	45 (26)	2.41 (1.29-4.61)	0.007
	NSCLC-NOS	50 (24)	44 (26)	2.73 (1.44-5.29)	0.002
	Missing	0 (0)	0 (0)		
Emphysema n (%)	No	98 (47)	79 (47)	1	
	Yes	62 (30)	52 (31)	1.04 (0.65-1.67)	0.87
	Missing	49 (23)	39 (23)		
Interstitial lung disease n (%)	No	145 (69)	116 (68)	1	
	Yes	15 (7)	15 (9)	1.25 (0.58-2.68)	0.56
	Missing	49 (23)	39 (23)		
Type of radiotherapy n (%)	Conventional	75 (36)	69 (41)	1	
	SABR	53 (25)	17 (10)	0.35 (0.18-0.65)	0.001
	sCRT	39 (19)	55 (32)	1.53 (0.91-2.6)	0.11
	cCRT	33 (16)	17 (10)	0.56 (0.28-1.08)	0.09
	CHART	9 (4)	12 (7)	1.45 (0.58-3.75)	0.43
	Missing	0 (0)	0 (0)		

**SqCC: Squamous cell carcinoma, Non-small cell lung cancer-not otherwise specified, SABR; Stereotactic ablative radiotherapy, sCRT: sequential chemoradiotherapy, cCRT: concurrent chemoradiotherapy, CHART: continuous hyperfractionated accelerated radiotherapy*

Table 5: Univariate and multivariate analysis for NLR/ALC and Survival.

Variable		Unadjusted OR (95% CI)	p-value	Adjusted OR* (95% CI)	p-value
Pre-treatment NLR	≤2.5	1		1	
	>2.5	1.46 (0.96-2.23)	0.08	1.71 (1.06-2.79)	0.03
Post-treatment NLR	≤5.5	1		1	
	>5.5	2.52 (1.66-3.83)	<0.001	2.36 (1.49-3.76)	<0.001
Change in NLR	≤3.6	1		1	
	>3.6	2.34 (1.53-3.62)	<0.001	2.41 (1.5-3.91)	<0.001
Pre-treatment ALC	≤2.2	1		1	
	>2.2	0.89 (0.55-1.44)	0.64	0.84 (0.49-1.44)	0.53
Post-treatment ALC	>0.8	1		1	

	≤0.8	2.98 (1.96-4.59)	<0.001	2.86 (1.76-4.69)	<0.001
Change in ALC	>0.9	1		1	
	≤0.9	1.48 (0.98-2.23)	0.06	1.35 (0.84-2.17)	0.22

**Adjusting for cofounders with univariate significance <0.1 (Overall stage, smoking status, pathological diagnosis and type of radiotherapyhistological sub-type & type of radiotherapy)*
***NLR: Neutrophil-lymphocyte ratio, ALC: Absolute lymphocyte count*

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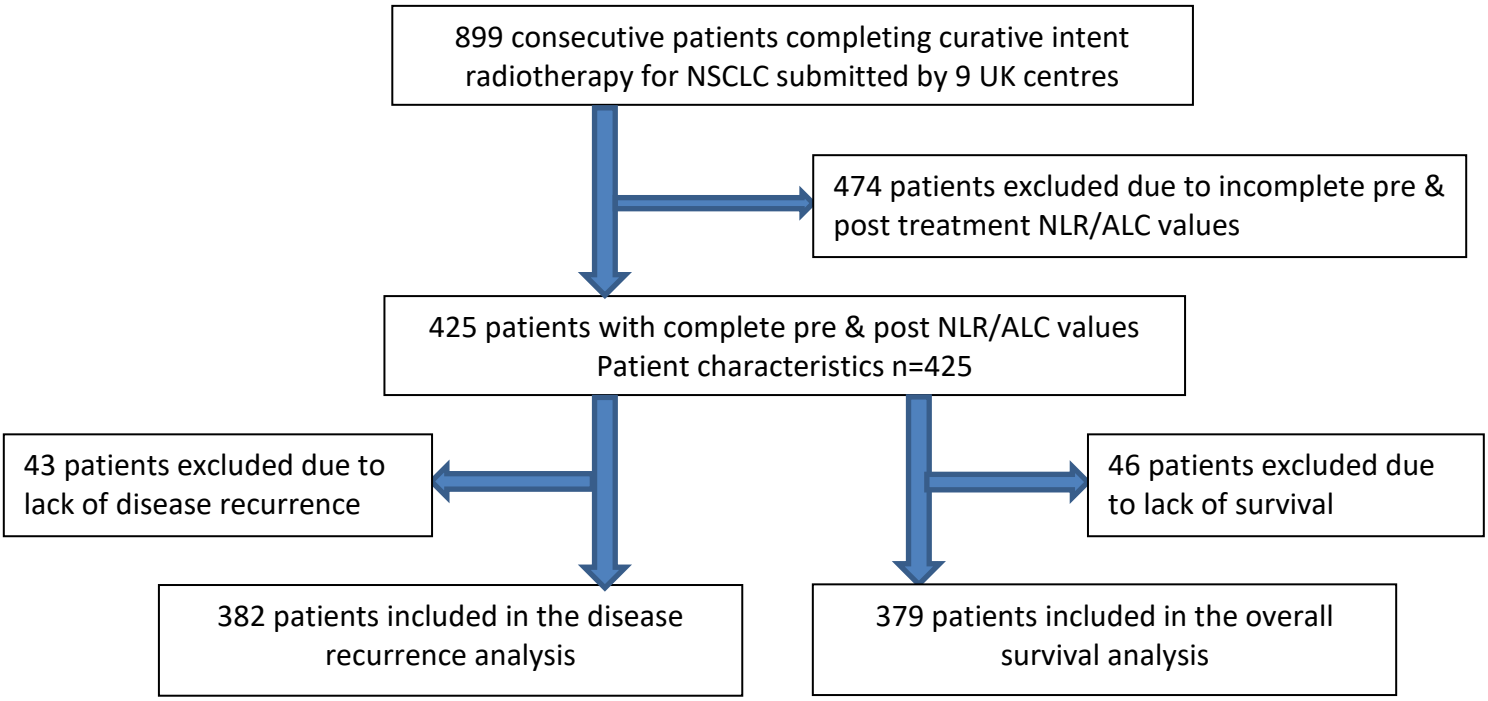
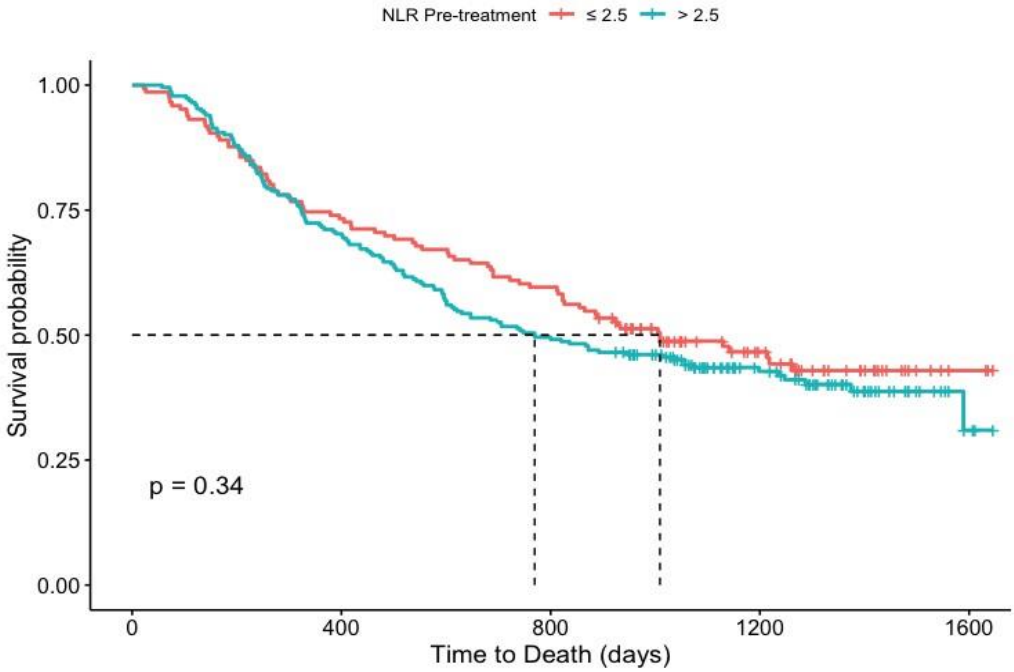
Figure 1: NLR/ALC study consort diagram



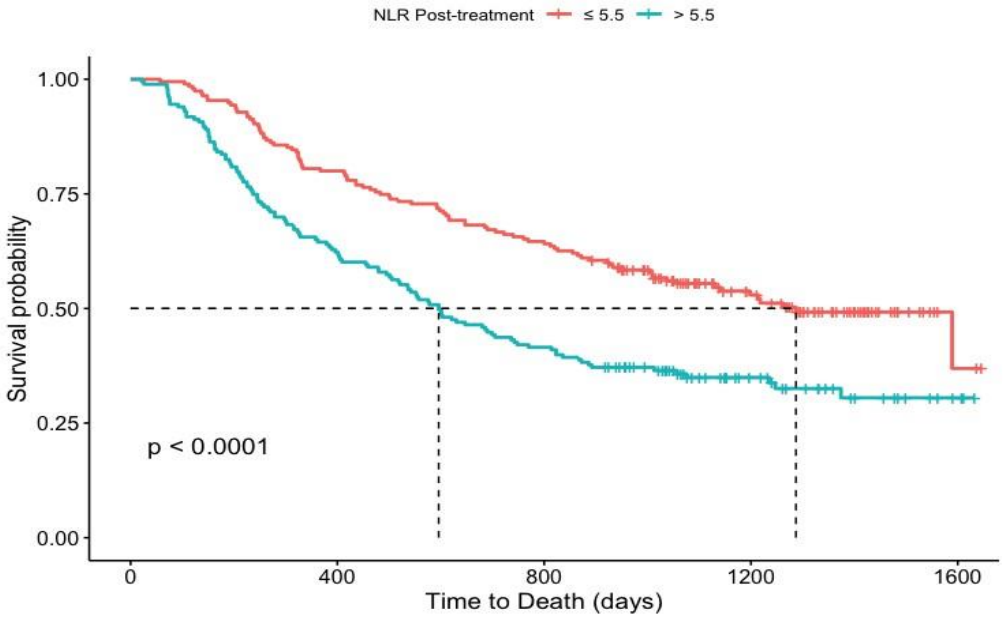
*NSCLC: non-small cell lung cancer, UK: United Kingdom,

Figure 1: Kaplan-Meier Curves for overall survival in high risk and low risk groups according to A) Pre-treatment NLR, B) Post-treatment NLR, C) change in NLR and D) Post-treatment ALC

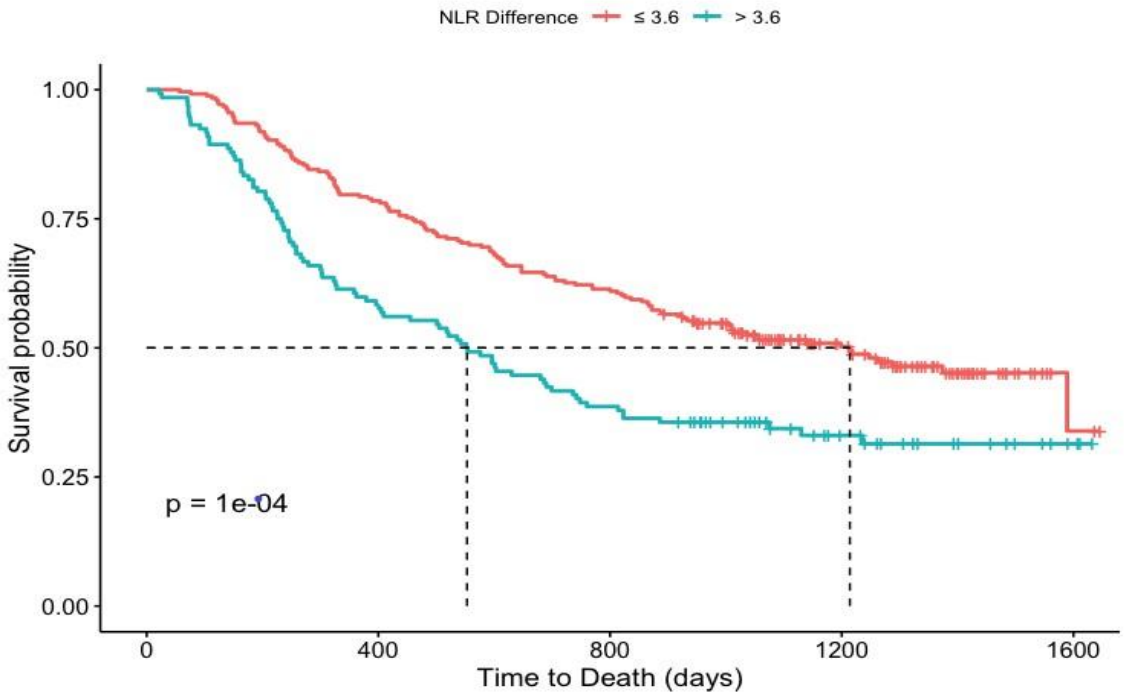
A)



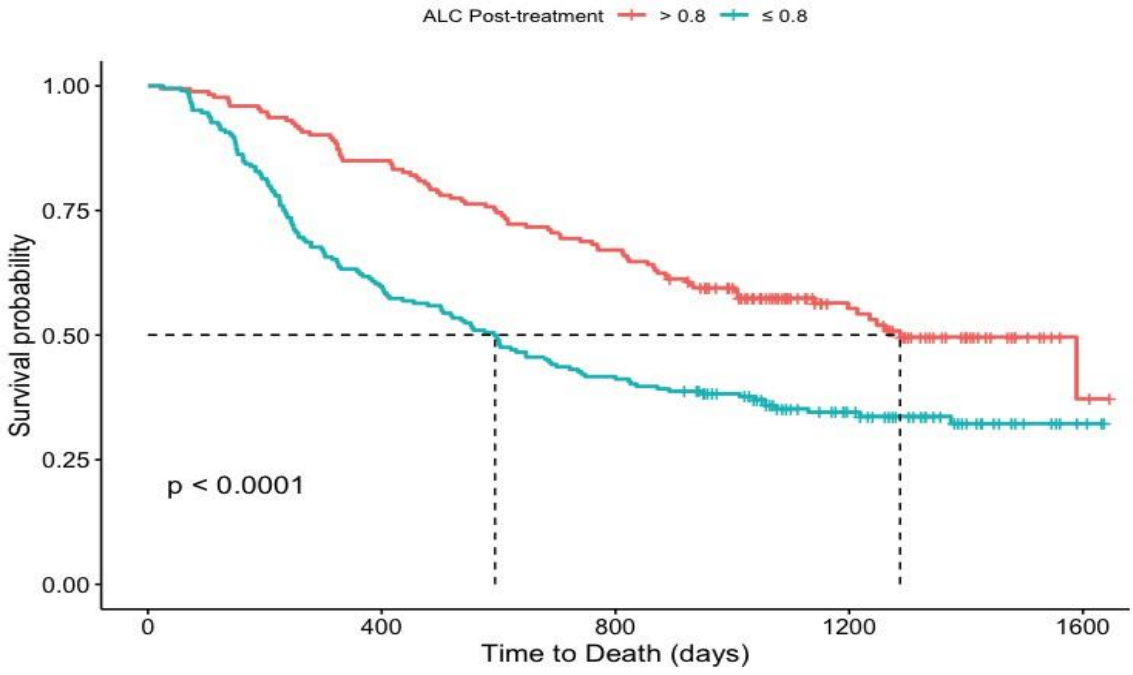
B)



C)


NLR Difference
≤ 3.6
> 3.6
1.00
0.75
0.50
0.25
0.00
Survival probability
p = 1e-04
0
400
800
1200
1600
Time to Death (days)

D)


ALC Post-treatment
> 0.8
≤ 0.8
1.00
0.75
0.50
0.25
0.00
Survival probability
p < 0.0001
0
400
800
1200
1600
Time to Death (days)