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CLINICAL INVESTIGATION

Pretreatment Risk Model for Radiation-Induced Lymphopenia Is Associated With Adjuvant Durvalumab Efficacy in Patients With Unresectable Stage III NSCLC

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Purpose: Severe radiation-induced lymphopenia (RIL) during concurrent chemoradiation therapy (CCRT) for NSCLC has been associated with poorer outcomes and reduced immunotherapy efficacy. Because RIL often develops late during CCRT, identifying patients at risk before treatment may be clinically relevant. This study aimed to develop and validate a nomogram based on pretreatment predictors for severe RIL, and secondarily to explore associations between predicted RIL risk and adjuvant durvalumab-associated survival.

Methods and Materials: A retrospective development cohort of consecutive patients with NSCLC treated with CCRT (2010-2019) was established, along with an independent external validation cohort from other institutions. A multivariable logistic

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[1]Peter S.N. van Rossum and Pim J.J. Damen made equal contributions to this study.

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regression model was developed to predict severe RIL, with internal and external validation. Survival analyses (progression-free and overall survival) were performed as exploratory, hypothesis-generating analyses stratified by predicted RIL risk and durvalumab use.

Results: Severe RIL was defined as an absolute lymphocyte count nadir of <0.24 K/μL. Among 451 patients, 164 (36%) developed severe RIL. Independent predictors were older age, cN3-stage, larger planning target volume, >30 radiation therapy fractions, higher mean lung dose, and lower baseline absolute lymphocyte count (c-statistic: 0.70). External validation (130 patients, 41 [32%] with severe RIL) yielded similar discrimination (c-statistic: 0.69). In exploratory analyses, durvalumab use was associated with improved survival in patients with a low predicted risk of severe RIL, whereas no statistically significant association was observed in those with a high predicted risk, in both cohorts.

Conclusions: We developed and externally validated a pretreatment prediction model for severe RIL during CCRT for NSCLC with consistent performance. In exploratory analyses, an association between durvalumab use and improved survival was observed in patients with a low predicted risk of severe RIL, but not in those with a high predicted risk. This model may help identify patients for lymphopenia-mitigating strategies and inform more personalized immunotherapy approaches, pending prospective validation.

Introduction

Lung cancer is the second most common type of cancer and the leading cause of cancer-related death worldwide.[1] For unresectable locally advanced non-small cell lung cancer (NSCLC), concurrent chemoradiation therapy (CCRT) is a curative-intent standard, improving overall survival (OS) compared with radiation therapy alone.[2] In the PACIFIC trial, adjuvant durvalumab (a programmed cell death-ligand 1 [PD-L1] inhibitor) after CCRT further improved survival (median OS 47.5 vs 29.1 months).[3]

Durvalumab enhances anti-tumor T-cell activity by blocking the PD-1/PD-L1 axis, and its efficacy depends on the presence of functional lymphocytes.[4] Although PACIFIC did not identify a clear nonbenefiting subgroup (aside from PD-L1 <1% and certain oncogenic drivers in post hoc analyses), not all patients derive clinical benefit.[5-7] Better selection would be highly valuable.

Radiation-induced lymphopenia (RIL) is common during thoracic radiation therapy, and a substantial proportion of patients develop severe (grade 3-4) RIL by the end of CCRT.[8] Severe RIL in patients undergoing CCRT has been associated with reduced immunotherapy efficacy in NSCLC.[9-11] Because severe RIL typically develops late during CCRT,[12] opportunities for lymphocyte-sparing adaptations are limited once it occurs. Therefore, a prediction model that identifies patients at high-risk of severe RIL before treatment (ie, a priori) would be valuable.

The primary aim of this study was to develop and externally validate a pretreatment prediction model for severe RIL (presented as nomogram) using baseline patient-, tumor-, and treatment-related predictors. A secondary aim was to explore durvalumab-associated outcomes across predicted RIL risk groups.

Methods and Materials

This retrospective cohort study was approved by the institutional review board. The requirement to obtain informed consent was waived. The study adhered to the Health Insurance Portability and Accountability Act and the principles of Good Clinical Practice.

Study population

From a single large tertiary referral center in the United States, consecutive patients with pathologically proven unresectable NSCLC were identified through manual review of electronic medical records. Patients were treated with CCRT from 2010 to 2019 or with CCRT followed by durvalumab from 2018 to 2019. Receipt of durvalumab was determined by calendar time, reflecting adoption as the standard of care, and was not based on PD-L1 status in this data set. Eligible patients were >18 years, had a World Health Organization (WHO) Performance Score ≤2, and a disease stage II or III. Patients were treated using either photon or proton-beam therapy (PBT). Chemotherapy consisted of carboplatin/cisplatin plus paclitaxel or pemetrexed. Patients with sequential chemoradiation were excluded, but induction chemotherapy before CCRT was allowed.

This data set was previously described in detail by Jing et al.[13] To increase sample size and variation to improve statistical power, we combined this data set with patients treated with CCRT for unresectable NSCLC as part of a randomized controlled trial at the same institution. This approach broadened the spectrum of fractionation schemes and dose distributions, which are potential key predictors in the model. Increasing heterogeneity in the training set improves statistical power and helps prevent overfitting to a single treatment pattern. As a result, our model's generalizability across different treatment patterns is enhanced.[14] Eligibility criteria were similar. Patients without a baseline absolute lymphocyte count (ALC) or without any ALC measurement during treatment were excluded.

External validation population

For the purpose of external validation of the anticipated prediction model, medical records from 3 centers in Europe

were screened for patients who underwent CCRT between June 2016 and December 2022 for unresectable NSCLC, with or without adjuvant durvalumab. In the participating European centers, durvalumab was implemented as standard of care over time and was administered irrespective of PD-L1 status. This data set was previously described in detail by Cortiula et al.[15] All patients received CCRT (60-66 Gy) using either photon or PBT, with ≥2 cycles of platinum-based doublet chemotherapy. Patients without a baseline ALC or without any ALC measurement during treatment were excluded. This validation cohort study was approved by the institutional review boards. The requirement to obtain informed consent was waived.

Outcome assessment

ALC values were obtained before CCRT (ie, at baseline) and during CCRT. The minimum ALC during CCRT was identified as ALCnadir. In lung cancer, most papers grade lymphopenia in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, which defines grade ≥3 lymphopenia as <0.5 K/μL. However, as the group with no grade ≥3 lymphopenia in our cohort was very small, choosing this outcome would greatly limit statistical power. Given the absence of a universally accepted or evidence-based ALCnadir threshold in this context, we adopted a data-driven approach. Similar to previous studies,[13,16] which also relied on cohort-specific and data-driven thresholds, we allowed our data to inform the optimal cut-off rather than applying predefined criteria that may not reflect prognostic separation in our cohort. Therefore, we determined the ideal ALCnadir threshold empirically, in an iterative process, to best distinguish survival in exploratory analyses after durvalumab versus no durvalumab and defined the primary outcome of severe RIL as an ALCnadir below this threshold. Because this approach is outcome-informed and may introduce circularity for subsequent durvalumab-related analyses, all durvalumab-associated survival findings are explicitly framed as exploratory/hypothesis-generating. As an additional sensitivity analysis, we evaluated the performance of the final prediction model for the commonly used CTCAE grade ≥3 definition (ALCnadir <0.5 K/μL).

Predictor selection

Only potential predictors that are typically known in clinical practice before the start of treatment (ie, at baseline) were selected. Potential predictors were selected based on published literature (ie, sex, age, WHO performance status, smoking status, tumor histology, clinical T-, N-, and M-stage, radiation therapy modality, planning target volume [PTV], total radiation therapy dose, number of radiation therapy fractions, mean lung dose [MLD], mean heart dose [MHD], induction chemotherapy [yes vs no], and baseline ALC),[17−21] supplemented by clinical reasoning (ie, disease status [primary tumor vs recurrence], tumor laterality, and tumor location). "Sex" was used as a biological variable and recorded as male or female based on medical record documentation.

Statistical analysis

Statistical modeling steps are described in detail in File E1. Severe RIL and nonsevere RIL groups were compared using Student's *t*test or Mann-Whitney *U* test for continuous variables, Pearson's χ^2 or Fisher's exact test for nominal categorical variables, and Mann-Whitney *U* tests for ordered categorical variables. In accordance with the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis statement,[22] missing data were handled with multiple imputation (20 data sets), and multivariable logistic regression assessed predictors of severe RIL. As a sensitivity analysis, we repeated model development as a complete-case analysis, applying the same univariable screening and backward Akaike's Information Criterion–based selection to evaluate whether the same predictors were retained and whether effect estimates and model performance substantially differed.

Model development involved first assessing pairwise Spearman's rank correlations among candidate predictors to reduce the risk of multicollinearity, by retaining only one of two correlated variables for further modeling when Spearman $\rho > .5$. Next, variables with a *P*value < .35 from univariable analysis were entered in a multivariable logistic regression model, as a deliberately liberal screening step to avoid prematurely excluding potentially relevant predictors that may become important after adjustment. Subsequently, backward stepwise elimination was applied based on Akaike's Information Criterion. The final model, presented as a nomogram, categorized patients into low- and high-risk groups for severe RIL.

Survival analyses were performed, including comparisons of progression-free survival (PFS) and OS with and without durvalumab. PFS and OS were calculated from the first day of CCRT. PFS was defined as time to first documented progression (local/regional/distant, based on routine clinical/radiologic assessment) or death, whichever occurred first (censored at last follow-up). OS was defined as time to death from any cause (censored at last follow-up). As a sensitivity analysis to assess robustness of the survival findings to immortal-time bias, we performed a 1-month post-CCRT landmark analysis, including only patients alive and progression-free ≥1 month after CCRT completion, and recalculated PFS and OS from the landmark timepoint.

Validation of the prediction model for severe RIL was performed internally using bootstrapping and externally by applying the model to a separate cohort. Model performance in terms of discrimination and calibration was assessed in both the development and external validation cohorts. Statistical significance was set at $P < .05$.

Results

The development cohort consisted of 451 eligible patients with NSCLC. Severe RIL was defined as an ALCnadir of <0.24 K/μL, and the cohort was divided into a group with (n = 164) and without (n = 287) severe RIL. Using the commonly applied CTCAE grade ≥3 definition (ALCnadir < 0.5 K/μL), 374 patients (82.9%) developed grade ≥3 lymphopenia, whereas 77 patients (17.1%) did not. The baseline characteristics and a comparison of the groups with versus without severe RIL (with ALCnadir 0.24 K/μL as cut-off) are presented in Table 1. Patients who experienced severe RIL more often had right-sided tumors, higher cN-stage, a larger PTV, a higher MLDMLD, MHD, and a lower baseline ALC. Thirty-two patients (19.5%) in the severe RIL group received adjuvant durvalumab, versus 85 patients (29.6%) in the nonsevere RIL group (P = .019). Compared with patients without severe RIL during CCRT, patients with observed severe RIL had worse PFS (HR, 1.55; 95% CI, 1.23-1.94) and worse OS (HR, 1.89; 95% CI, 1.49-2.39) (Fig. E1). The benefit of durvalumab appeared to be primarily observed in the group without severe RIL, whereas no significant association with benefit was seen in patients with observed severe RIL (Fig. E2).

Results of univariable logistic regression analysis for severe RIL are demonstrated in Table 2. High bivariable correlation was observed among baseline factors MLD and MHD (ρ > .5), and resulted in the exclusion of MHD in subsequent modeling steps. After entering variables into a full multivariable logistic regression model and performing stepwise backward elimination, the final prediction model included 6 independent predictors of severe lymphopenia (ie, age, cN-stage, PTV, number of fractions, MLD, and baseline ALC; Table 2). An increased risk of severe RIL was observed in patients with higher age (per 10 years, adjusted OR 1.27; 95% CI, 1.01-1.61), cN3 disease (adjusted OR 1.70; 95% CI, 1.01-2.87), a larger PTV (per 100 mL, adjusted OR 1.10; 95% CI, 1.03-1.18), number of fractions >30 (adjusted OR 1.66; 95% CI, 1.08-2.54), or a higher MLD (per Gy, adjusted OR 1.09; 95% CI, 1.03-1.16). Higher baseline ALC (per 1.0 K/μL increase, adjusted OR 0.61; 95% CI, 0.44-0.85) appeared protective of severe RIL. The discriminatory model performance was fair with a corrected c-statistic after internal validation of 0.70 (95% CI, 0.65-0.75; Fig. 1A). Internal model calibration among risk quartiles was good with mean predicted risks of severe RIL of 16%, 29%, 41%, and 60%, corresponding to observed risks of 17%, 24%, 45%, and 60%, respectively (Fig. 1C).

In a complete-case sensitivity analysis (n = 392 with severe RIL in 138), the same 6 predictors were retained, with very similar effect estimates (maximum absolute difference in ORs, 0.00-0.11) and a corrected c-statistic of 0.71. In another sensitivity analysis, when applying the final model to predict CTCAE grade ≥3 lymphopenia (ALCnadir < 0.5 K/μL), discrimination was excellent with a c-statistic of 0.82 (95% CI, 0.77−0.86).

For the external validation cohort, 130 patients were found eligible for inclusion, of which 41 (32%) experienced severe RIL during CCRT. Photon-based radiation therapy was used in 105 (81%) and PBT in 25 (19%) of patients. The number of fractions was ≤30 in 109 patients (84%). Chemotherapy predominantly consisted of a platinum/etoposide doublet. Adjuvant durvalumab was administered in 65 patients (50%). The application of the developed prediction model to the external cohort resulted in an external c-statistic of 0.69 (95% CI, 0.58−0.79) for predicting severe RIL (Fig. 1B). External model calibration was modest, with some underestimation of the actual risk of severe RIL in the higher risk quartiles (Fig. 1D).

The prediction model was presented as a nomogram with a sum score ranging from 0 to 40 (Fig. 2). Among 169 patients in the development cohort with a nomogram sum score <20, only 33 (19.5%) had observed severe RIL, and adjuvant durvalumab was administered in 68 (40%). In these patients with a low predicted risk of severe RIL, durvalumab (vs no durvalumab) was associated with a significantly improved PFS (HR, 0.53; 95% CI, 0.34-0.84; Fig. 3A) and OS (HR, 0.35; 95% CI, 0.18-0.68; Fig. 3C). In contrast, among the 282 patients with a high predicted risk of severe RIL (nomogram sum score ≥ 20), 131 (46.5%) had observed severe RIL, and adjuvant durvalumab in 49 patients (17%) demonstrated no significant association with PFS compared with patients without durvalumab (HR, 0.99; 95% CI, 0.69-1.42; Fig. 3B) or OS (HR, 0.82; 95% CI, 0.53-1.26; Fig. 3D). A 1-month post-CCRT landmark sensitivity analysis yielded similar results, showing that durvalumab remained associated with improved PFS and OS in the low predicted risk group (n = 158; 58 durvalumab), but not in the high predicted risk group (n = 247; 48 durvalumab; Fig. 3).

In the external validation cohort, among 91 patients with a low predicted risk of severe RIL, durvalumab (vs no durvalumab) was associated with a significantly improved PFS (HR, 0.48; 95% CI, 0.26-0.89; Fig. 4A) and OS (HR, 0.43; 95% CI, 0.18-0.99; Fig. 4C). On the contrary, among 39 patients with a high predicted risk of severe RIL, adjuvant durvalumab demonstrated no significant difference in terms of PFS (HR, 0.70; 95% CI, 0.29-1.64; Fig. 4B) or OS (HR, 0.57; 95% CI, 0.23-1.44; Fig. 4D).

Discussion

This study developed and internally and externally validated a pretreatment model to predict severe RIL during CCRT for NSCLC. A lower predicted risk of severe RIL was associated with benefit from adjuvant durvalumab, whereas a higher predicted risk was not. Therefore, this prediction model may help identify patients who could benefit from lymphopenia-mitigating strategies and may support a more selective (personalized) use of durvalumab to optimize efficacy, toxicity, and costs. These durvalumab-related findings

Table 1 Baseline characteristics

Characteristic	ALCnadir ≥ 0.24 K/μL (n = 287)	ALCnadir < 0.24 K/μL (n = 164)	*P* value
Male sex	164 (57.1%)	82 (50.0%)	.143
Age (y)	65.7 ± 9.6	66.6 ± 8.5	.324
Performance status			.630
WHO 0	72 (32.9%)	38 (33.0%)	
WHO 1	143 (65.3%)	70 (60.9%)	
WHO 2	4 (1.8%)	7 (6.1%)	
Missing	*68*	*49*	
Previous/current smoker	214 (74.6%)	122 (74.4%)	.967
Disease status			.293
Primary tumor	270 (94.1%)	158 (96.3%)	
Recurrence	17 (5.9%)	6 (3.7%)	
Tumor lateralization			.049*
Right lung	159 (55.6%)	109 (66.9%)	
Left lung	122 (42.7%)	53 (32.5%)	
Mediastinum	5 (1.7%)	1 (0.6%)	
Tumor location			.427
Upper lobe	180 (63.6%)	103 (63.6%)	
Middle lobe	24 (8.5%)	9 (5.6%)	
Lower lobe	74 (26.1%)	49 (30.2%)	
Mediastinum	5 (1.8%)	1 (0.6%)	
Missing	*4*	*2*	
Pathologic type			.267
Adenocarcinoma	149 (51.9%)	98 (59.8%)	
Squamous cell carcinoma	111 (38.7%)	54 (32.9%)	
Other	27 (9.4%)	12 (7.3%)	
cT-stage			.719
cT1	53 (19.8%)	27 (17.2%)	
cT2	101 (37.7%)	62 (39.5%)	
cT3	53 (19.8%)	32 (20.4%)	
cT4	61 (22.8%)	36 (22.9%)	
Missing	*19*	*7*	
cN-stage			.001*
cN0-1	70 (25.1%)	28 (17.5%)	
cN2	163 (58.4%)	83 (51.9%)	
cN3	46 (16.5%)	49 (30.6%)	
Missing	*8*	*4*	
cM-stage			.716
cM0	275 (97.9%)	158 (98.8%)	
cM1	6 (2.1%)	2 (1.2%)	
Missing	*6*	*4*	
Radiation therapy modality			.209
IMRT	100 (34.8%)	72 (43.9%)	
VMAT	103 (35.9%)	46 (28.0%)	
PSPT	68 (23.7%)	39 (23.8%)	
IMPT	16 (5.6%)	7 (4.3%)	
PTV (mL)	430 (287-654)	552 (390-860)	<.001*
Missing	*21*	*19*	
Radiation dose (Gy)	66 (60-74)	66 (60-74)	.820
Number of radiation fractions			.066
≤30 fractions	148 (51.6%)	68 (41.5%)	
31-36 fractions	67 (23.3%)	53 (32.3%)	
37 fractions	72 (25.1%)	43 (26.2%)	

(*Continued*)

Table 1 (*Continued*)

Characteristic	ALCnadir ≥ 0.24 K/μL (n = 287)	ALCnadir < 0.24 K/μL (n = 164)	*P* value
Mean lung dose (Gy)	12.5 ± 4.6	16.1 ± 4.1	<.001*
Mean heart dose (Gy)	6.3 (2.3-14.7)	13.0 (7.2-18.4)	.001*
Missing	*172*	*81*	
Induction chemotherapy	34 (11.8%)	18 (11.0%)	.781
Baseline ALC (K/μL)	1.79 ± 0.69	1.59 ± 0.68	.003*
Missing	*4*	*5*	

Abbreviations: 3DCRT = 3-dimensional conformal radiation therapy; ALC = absolute lymphocyte count; IMPT = intensity modulated proton therapy; IMRT = intensity modulated radiation therapy; PSPT = passive scattering proton therapy; PTV = planning target volume; RT = radiation therapy; VMAT = volumetric modulated arc therapy.
* Statistically significant difference.

Table 2 Univariable and multivariable logistic regression analysis for ALCnadir <0.24 K/μL

	Univariable analysis		Multivariable analysis	
Characteristic	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
Male sex	0.75 (0.51-1.10)	.143	-	-
Age (per 10 y)	1.11 (0.90-1.37)	.323	1.27 (1.01-1.61)	.048*
Performance status				
WHO 0-1	Ref	.050	-	-
WHO 2	3.48 (1.00-12.2)			
Smoking status				
Never	Ref	.967	-	-
Previous/current	0.99 (0.64-1.54)			
Disease status				
Primary tumor	Ref	.297	-	-
Recurrence	0.60 (0.23-1.56)			
Tumor lateralization				
Right lung	Ref	.020*	-	-
Left lung (or mediastinum)	0.62 (0.42-0.93)			
Tumor location				
Upper lobe	Ref	.510	-	-
Lower lobe	1.16 (0.75-1.79)	.191	-	-
Middle lobe (or mediastinum)	0.60 (0.28-1.29)			
Pathologic type				
Adenocarcinoma	Ref	.108	-	-
SCC (or other)	0.73 (0.49-1.07)			
cT-stage				
cT1	Ref	.515	-	-
cT2	1.21 (0.69-2.11)	.602	-	-
cT3	1.19 (0.63-2.24)	.642	-	-
cT4	1.16 (0.62-2.15)			
cN-stage				
cN0-2	Ref	.001*	Ref	.046*
cN3	2.24 (1.41-3.55)		1.70 (1.01-2.87)	
Radiation therapy modality				
IMRT	Ref	.042*	-	-
VMAT	0.62 (0.39-0.98)	.254	-	-
PSPT/IMPT	0.76 (0.48-1.22)			

(*Continued*)

Table 2 (*Continued*)

	Univariable analysis		Multivariable analysis	
Characteristic	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
PTV (per 100 mL)	1.16 (1.08-1.23)	<.001*	1.10 (1.03-1.18)	.008*
Radiation dose (per 10 Gy)	1.02 (0.73-1.43)	.900	-	-
Number of radiation fractions				
≤30 fractions	Ref	.039*	Ref	.020*
>30 fractions	1.50 (1.02-2.21)		1.66 (1.08-2.54)	
Mean lung dose (per Gy)	1.14 (1.08-1.19)	<.001*	1.09 (1.03-1.16)	.003*
Log (mean heart dose)†	1.51 (1.16-1.96)	.002*	-	-
Induction chemotherapy	0.92 (0.50-1.68)	.781	-	-
Baseline ALC (K/μL)	0.63 (0.47-0.86)	.003*	0.61 (0.44-0.85)	.003*

Abbreviations: ALC = absolute lymphocyte count; CCRT = concurrent chemoradiation therapy; IMPT = intensity modulated proton therapy; IMRT = intensity modulated radiation therapy; PSPT = passive scattering proton therapy; PTV = planning target volume; RT = radiation therapy; SCC = squamous cell carcinoma.

* Statistically significant association.

† Better fit with logarithmic transformation.

Logistic regression formula of multivariable model: ln(p/(1-p)) = -3.651 + 0.238*(Age/10) + 0.532*cN-stage ["cN0-2"=0, "cN3"=1] + 0.098*(PTV/100) + 0.507*Fractions ["≤30"=0, ">30"=1] + 0.0=88*Mean lung dose − 0.489*Baseline ALC.

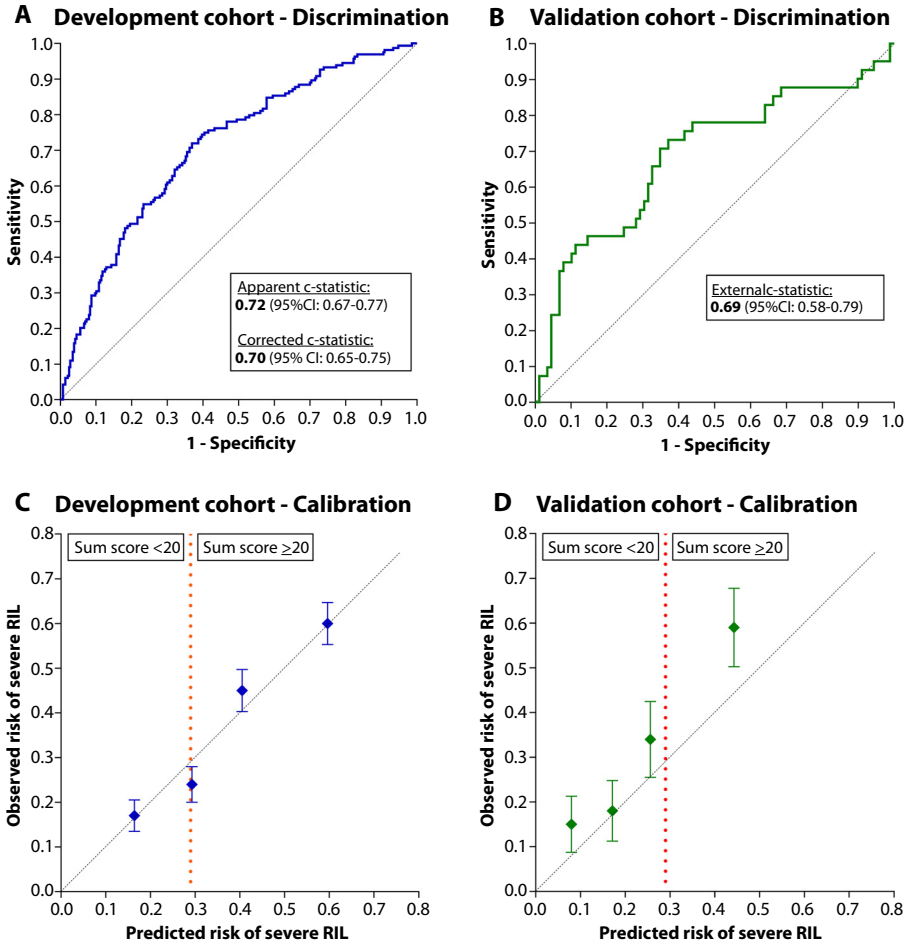

Fig. 1. The discriminatory model performance and calibration plot of the model in the development cohort (A, C) and external validation cohort (B, D).

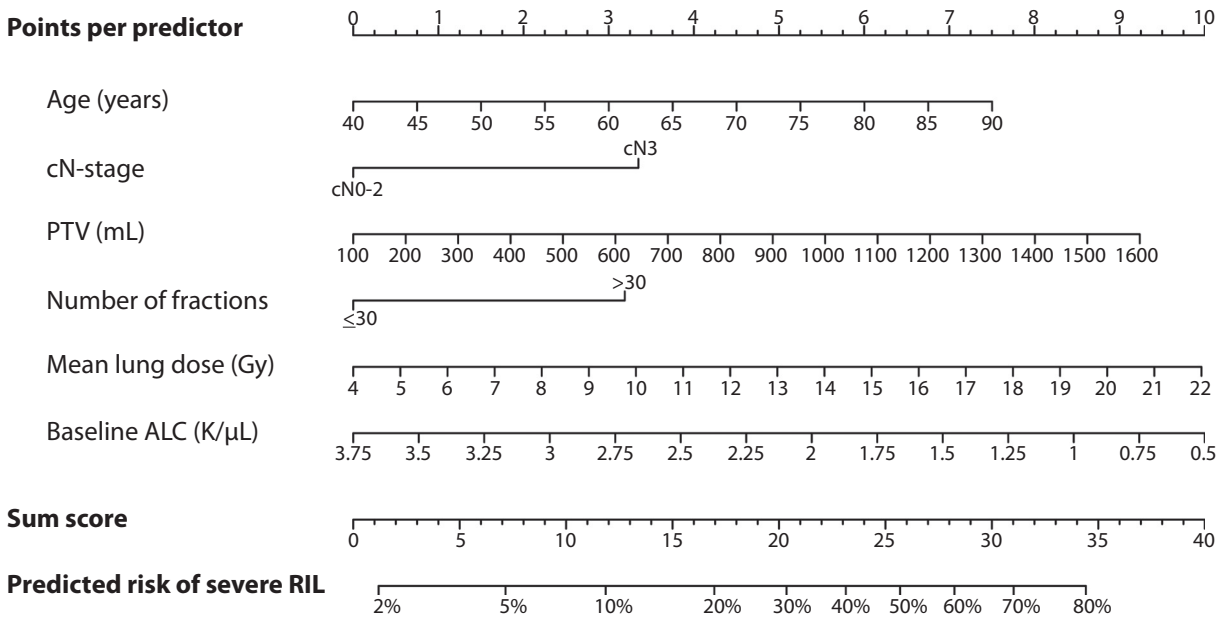

Fig. 2. Pretreatment clinical nomogram to predict the risk of severe RIL (ALCnadir < 0.24 K/μL) during CCRT in patients with NSCLC. The indicated points at the top of the figure represent the assigned points for each variable. By adding up these points, the predicted risk of severe RIL can be determined by drawing a straight vertical line from the sum score line to the bottom line of the figure.

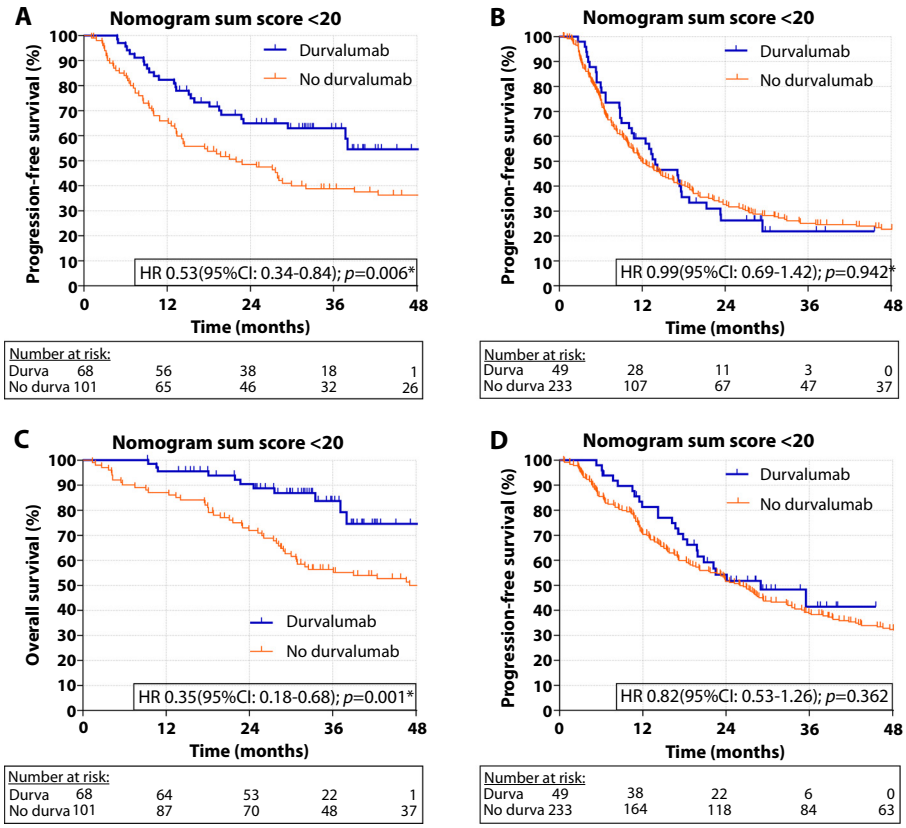

Fig. 3. Kaplan-Meier analysis of PFS (A, B) and OS (C, D) in patients who received adjuvant durvalumab versus patients who did not, stratified by low predicted risk of severe RIL (ie, nomogram sum score < 20; A, C) and high predicted risk of severe RIL (ie, nomogram sum score ≥ 20; B, D) in the study population.

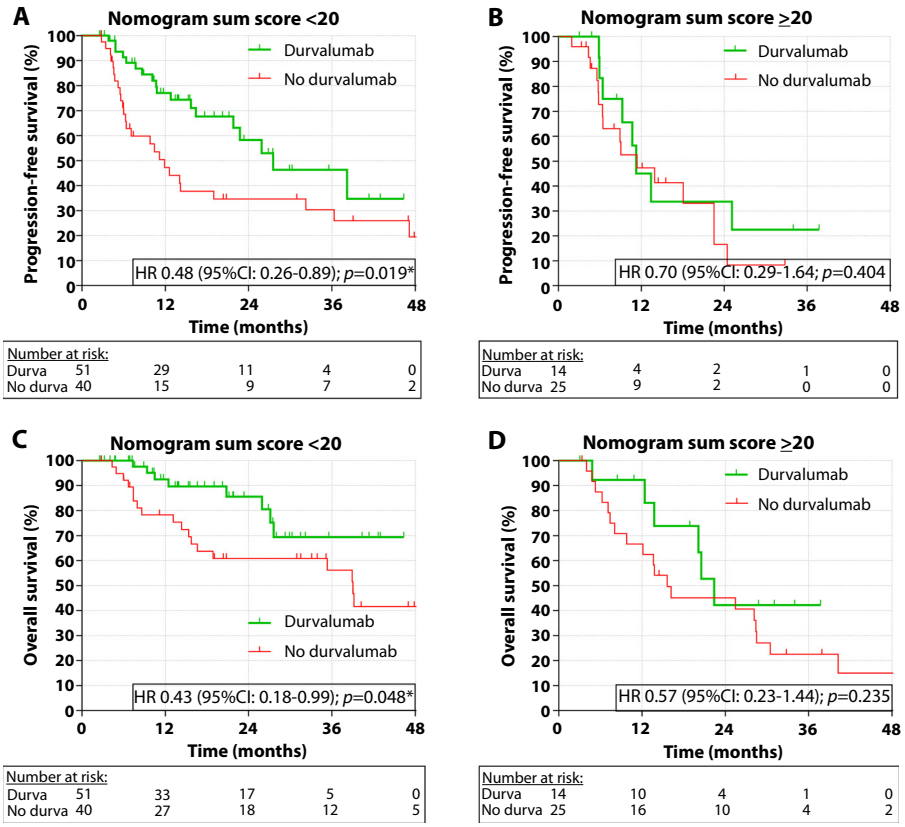

Fig. 4. Kaplan-Meier analysis of PFS (A, B) and OS (C, D) in patients who received adjuvant durvalumab versus patients who did not, stratified by low predicted risk of severe RIL (ie, nomogram sum score < 20; A, C) and high predicted risk of severe RIL (ie, nomogram sum score ≥ 20; B, D) in the validation population.

should be interpreted as exploratory and hypothesis-generating, given the observational study design.

Severe RIL is a common toxicity in patients with lung cancer treated with CCRT, with grade ≥3 RIL observed in 45%-64%.[8,20,23,24] A meta-analysis of four lung cancer cohorts linked grade ≥3 RIL to worse OS (adjusted HR, 1.52; 95% CI, 1.01-2.29).[8] Another meta-analysis (10 OS studies; 7 PFS studies) confirmed a negative impact on OS (HR, 1.59; 95% CI, 1.40-1.81) and PFS (HR, 2.10; 95% CI, 1.57-2.81).[24] In our development cohort, grade ≥3 RIL occurred in 82.9%. We chose a data-driven threshold for severe RIL because the high incidence of grade ≥3 RIL would reduce power for logistic regression model development and particularly limit risk-stratified survival analyses because of small numbers in the nonevent group. Nevertheless, when applying our final model to the grade ≥3 endpoint, discrimination remained excellent (c-statistic 0.82; 95% CI, 0.77-0.86), supporting robustness of the model across outcome definitions.

In previous studies, severe RIL was strongly associated with fewer fractions (ie, hypofractionation), shorter treatment time,[24] and dosimetric factors, such as MLD, MHD, and low-dose (eg, V5Gy) heart/lung exposure.[16,23,25,26] Other reported predictors include tumor volume,[25] older age,[20,26] lower baseline ALC,[20,23,27] and higher tumor stage.[25] Abravan et al[20] used image-based data mining in 901 patients with lung cancer and identified thoracic vertebrae V20Gy, MLD, and MHD as the strongest predictors of grade ≥3 RIL.

In our study, we observed that severe RIL was associated with worse PFS and OS. We were able to identify, before treatment, patients at high predicted risk of severe RIL in whom no significant association with durvalumab benefit was observed. Multivariable modeling confirmed older age, higher cN-stage, larger PTV, >30 radiation fractions, higher MLD, and lower baseline ALC as independent predictors. Older age and lower baseline ALC may reflect reduced lymphocyte reserve and/or greater tumor-induced immune suppression.[28–30] Higher cN-stage, larger PTV, >30 fractions, and higher MLD likely reflect greater tumor burden and greater cumulative irradiation of the blood pool, lymphoid tissues, and bone marrow, increasing the risk of lymphocyte depletion.[12,30–32]

Selecting patients with NSCLC who benefit from durvalumab remains challenging. In PACIFIC, no clear nonbenefiting prespecified subgroup was identified beyond the PD-L1 <1% signal.[3] Lymphocyte depletion may be relevant because low lymphocyte counts can reduce immunotherapy efficacy.[9-11,33] A meta-analysis on 1130 patients with lung cancer treated with immunotherapy linked severe RIL (ALCnadir grade ≥ 3) to poorer PFS (HR, 2.05; 95% CI, 1.62-2.60) and OS (HR, 2.69; 95% CI, 2.10-3.43).[33] Smaller

studies similarly suggest that peri- or preimmunotherapy lymphopenia is associated with worse outcomes, with prior radiation therapy increasing lymphopenia risk.[9-11]

In this study, the multivariable prediction model appeared to stratify durvalumab-associated outcomes better than observed ALCnadir alone,[13] likely because it integrates tumor extent (eg, cN-stage), baseline immune reserve (eg, age and baseline ALC), and anticipated immune cell killing (eg, PTV and MLD). Unlike observed ALCnadir, all model variables are known pretreatment, which may enable proactive treatment adaptation to mitigate RIL. However, the primary severe RIL threshold was outcome-informed and could inflate apparent stratification of durvalumab-associated outcomes; therefore, these findings require prospective confirmation.

Several RIL prediction models have been proposed.[17,20,34,35] Van Rossum et al[36] externally validated 2 models, with a PTV-based model[17] outperforming a dosimetry-based model[20] in NSCLC. Similar to our model, these tools aim to identify high-risk patients for lymphopenia mitigation. Our study additionally explored durvalumab-associated outcomes across predicted risk groups, which requires prospective confirmation.

Our observation that the durvalumab-associated benefit was restricted to patients with a low predicted risk of severe RIL is hypothesis-generating. A plausible mechanism is that severe RIL impairs quantitative and qualitative immune reconstitution, including reduced T-cell receptor diversity, which may limit tumor antigen recognition.[37−39] Determining whether severe RIL is merely prognostic or also predictive for durvalumab benefit requires prospective studies, ideally testing lymphopenia mitigation strategies and evaluating immunotherapy outcomes.

Strategies to mitigate RIL aim to reduce radiation exposure to circulating blood and lymphoid organs (eg, large vessels, heart, lungs, lymph nodes, spleen, and thymus).[8,40] Although standardized constraints are lacking, the "as low as reasonably achievable" principle should guide practice.[40] Potential approaches include smaller fields, shorter treatment duration, hypofractionation, and lower integral dose. Proton therapy may reduce integral dose. In esophageal cancer, reduced high-grade lymphopenia has been reported and later confirmed in a phase II trial.[15,41−43] In lung cancer, we observed no difference between photons and protons, consistent with a randomized trial using passive scattering protons,[14] whereas modern IMPT may better preserve lymphocytes.[44] Adaptive radiation therapy may further reduce margins and radiation exposure to lymphocytes.[45,46] Experimental strategies (eg, FLASH IL-7, lymphocyte harvesting/reinfusion) are promising but require randomized evaluation.[47-49]

A few limitations apply. This was a retrospective observational study. Therefore, no causal inferences can be made regarding predictors and RIL, or RIL and survival or durvalumab efficacy. The primary ALCnadir threshold for severe RIL was outcome-informed because of the absence of a standard definition, and durvalumab-related analyses are exploratory only. Other predictors (eg, PD-L1, EGFR/ALK status, and additional lung/heart dose parameters) were unavailable, and generalizability might be limited to high-volume academic centers. Finally, the external cohort had <100 events, limiting precision, particularly in the high predicted risk group. Moreover, the nomogram is best interpreted for risk stratification rather than precise individual-level risk estimates, and comparisons in the high predicted risk group are further limited by reduced calibration performance at the upper end of the risk scale and smaller subgroup sizes. Therefore, further external validation is warranted.

In conclusion, this study developed and externally validated a pretreatment model to predict severe RIL during CCRT for NSCLC. An association between durvalumab and improved survival was observed in patients with a low predicted risk of severe RIL, but not in patients with a high predicted risk. This model may support patient selection for lymphopenia-mitigating strategies and more personalized use of immunotherapy, pending prospective validation.

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