Original Study

Lung Immune Therapy Evaluation (LITE) Risk, a Novel Prognostic Model for Patients With Advanced Non-Small Cell Lung Cancer Treated With Immune Checkpoint Blockade

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Abstract

In this cohort study of 495 patients with NSCLC, a prognostic scoring system was derived and externally validated. Patients were parsed into 3 discrete risk groups. The final model included baseline Eastern Oncology Cooperative Group performance status, derived neutrophil to lymphocyte ratio and lactate dehydrogenase. A simple prognostic scoring tool utilizing accessible clinical data can discriminate survival outcomes in patients with treated with single-agent ICI.

Introduction/Background: Immune checkpoint inhibitors (ICI) have revolutionized non-small cell lung cancer (NSCLC). We aimed to identify baseline characteristics, that are prognostic factors for overall survival (OS) in patients with NSCLC treated with ICI monotherapy, in order to derive the Lung Immune Therapy Evaluation (LITE) risk, a prognostic model. **Materials and Methods:** Multi-center observational cohort study of patients with advanced NSCLC that received ≥1 dose of ICI monotherapy. The training set (n=342) consisted of patients with NSCLC who received first line ICI. The test set (n=153) used for external validation was a discrete cohort of patients who received second line ICI. 20 candidate prognostic factors were examined. Penalized Cox regression was used for variable selection. Multiple imputation was used to address missingness. **Results:** Three baseline characteristics populated the final model: ECOG (0, 1 or ≥2), lactate dehydrogenase>upper limit of normal, and derived neutrophil to lymphocyte ratio ≥3. Patients were parsed into 3 risk groups; favorable (n=146, risk score 0-1), intermediate (n=101, risk score 2) and poor (n=95, risk score ≥3). The c-statistic of the training cohort was 0.702 and 0.694 after bootstrapping. The test cohort c-statistic was 0.664. The median OS for favorable, intermediate and poor LITE risk were; 28.3 months, 9.1 months and 2.1 months respectively. Improving LITE risk group was associated with improved OS, intermediate vs favorable HR 2.08 (95%CI 1.46-2.97, $P < .001$); poor vs favorable HR 5.21 (95%CI 3.69-7.34, $P < .001$). **Conclusion:** A simple prognostic model, utilizing accessible clinical data, can discriminate survival outcomes in patients with advanced NSCLC.

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Introduction

Immune checkpoint inhibitors (ICIs) have drastically altered the treatment paradigm for non-small cell lung cancer (NSCLC) over the past decade.[1,2] However, studies of real-world populations suggests the existence of a concerning efficacy-effectiveness gap.[3-6] As such, robust prognostic scoring tools are needed to aid with risk stratification in order to engage in data-driven shared decision making with patients. Given this evidence gap, we sought to derive and validate a simple and clinically accessible prognostic model, termed the lung immune therapy evaluation (LITE)-risk, to stratify patients with advanced NSCLC treated with ICI monotherapy.

Methods

Study Design

The Alberta Immunotherapy Database (AID) is a multi-center observational cohort study. Baseline demographic, clinical and tumor characteristics, alongside survival outcomes are identified using a standard template and collected retrospectively.[4,5] This database captures outcomes from patients from the time of ICI monotherapy initiation. The training cohort consisted of treatment naïve patients with histologically confirmed advanced NSCLC that received first line (1L) pembrolizumab monotherapy, primarily with PD-L1 tumor proportion score (TPS) $\geq$ 50%. The test cohort included patients treated with nivolumab or atezolizumab in the second line (2L). We sought to identify baseline characteristics at ICI commencement, independently associated with inferior OS in order to derive a prognostic risk model, initially using the training cohort and then validated on the test cohort. 20 candidate variables were examined based on known clinically accessible, baseline characteristics, with reported prognostic or predictive associations with OS from the contemporary literature.[5-10]

Patients initiated treatment between January 2010 and December 2019, with data analysis undertaken in February 2022. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed. This study was approved by the Health Research Ethics Board of Alberta – Cancer Committee (HREBA.CC-19-0380).

Outcomes of Interest

The primary endpoint was overall survival (OS), defined as the time from commencement of ICI to death from any cause or date of last follow-up.

Statistical Analysis

Baseline laboratory markers were dichotomized based on their relationship to normal ranges and continuous variables based on conventional cut points. All variables were binary in nature except Eastern Cooperative Oncology Group (ECOG) performance status, where patients were stratified as ECOG = 0, ECOG = 1, or ECOG $\geq$ 2. For this study, we used least absolute shrinkage and selection operator (LASSO) Cox regression for variable selection. LASSO is a statistical method that performs parsimonious variable selection and helps to improve the generalizability of the model to external datasets by reducing the degree of overfitting.[11] To deal with missing data, we used multiple imputations by chained equations (MICE). This approach is commonly used and is less biased compared to a complete case analysis that excludes all patients with missing data.[12] LASSO Cox regression was fit on the original dataset through 10-fold cross-validation to identify the shrinkage parameter λs that yielded a 3-, 4-, or 5-variable model. Cross-fold validation is a resampling method that uses different portions of the dataset to for testing and training in order to predict how a model will perform on an independent dataset that was not used to derive it. In this way an attempt is made to avoid overfitting or selection bias.

The shrinkage parameter controls the degree to which the model coefficients are shrunk toward zero and number of covariates selected. Model performance was assessed using Harrell's C-statistic. The C-statistic gives the probability a randomly selected patient who experienced an event (death) had a higher risk score than a patient who had not experienced the event. A value of 0.5 means that the model is no better than predicting the outcome than random chance, whereas values of 0.7 or higher indicate a good model.

The prognostic risk model generated was built with independent prognostic factors using the training cohort and then validated using the test cohort. It has been established that prognostic models such as this perform better on data on that informed model construction compared to new data.[13] Because of this, internal and external validation are required. Internal validation was carried out internally using 500 iterations of bootstrapped samples in the training cohort. Bootstrapping is a statistical procedure that resamples a single dataset with replacement in order to create many simulated samples.[14] The same variable selection process through LASSO Cox regression was carried out in each bootstrap sample to develop a prognostic model. C-statistics of this model on the bootstrap sample (bootstrap performance) and in the original sample (test performance) were calculated. Optimism, the difference between training error and test error, was estimated as the mean difference between the bootstrapped performance and the test performance after 500 iterations. External validation was conducted using an independent test set comprised of individuals who initiated 2L systemic therapy with an ICI following a 1L therapy other than pembrolizumab. No patients in the training set were included in the test set. OS curves were estimated using the Kaplan-Meier method.

All statistical analyses were performed in R v.4.0.2 (R, Vienna, Austria). All statistical tests were 2 sided with a significance level of $\leq$0.05.

Results

342 systemic therapy naïve patients receiving pembrolizumab were examined in the training cohort. The external validation cohort (n=153) consisted of patients treated in the 2L with nivolumab (95.4%) or atezolizumab (4.6%) monotherapy As per Table 1, notable significant differences between the test cohort and training cohorts included a lower proportion of patients with adenocarcinoma (62.1% vs 72.8% $P = .05$) and PD-L1 TPS $\geq$ 50% (2.6% vs 95% $P < .0001$). More patients in the validation cohort had metastatic disease at ICI initiation (92.2% vs 84% $P = .04$) and a lactate dehydrogenase (LDH) > upper limit of normal (ULN) (41% vs 29.3% $P = .029$).

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Table 1 Baseline Characteristics of Training & Test Cohorts

	Training Cohort n=342	Test Cohort n=153	*P* Value
Mean Age (Range)	69.2 (33.2 - 88.9)	66.5 (33.1 - 85.2)	.24
Missing	0	0	
Gender (%)			
Female	177 (51.6)	81 (52.9)	.78
Male	166 (48.4)	72 (47.1)	
Missing	0	0	
Mean BMI (Range)	26.2 (14.5 - 42.4)	26.0 (15.6 - 44.0)	.97
Missing	10	2	
Histology			
Squamous	74 (21.6)	43 (28.1)	
Adenocarcinoma	249 (72.8)	95 (62.1)	
Other	19 (5.6)	15 (9.8)	**.05**
Missing	0	0	
Smoker			
Yes	305 (89.2)	135 (91.2)	.57
Missing	14	5	
ECOG			
0	51 (14.9)	16 (10.5)	
1	201 (58.6)	84 (54.9)	
2	75 (21.9)	43 (28.1)	
3	15 (4.3)	6 (3.9)	.056
Missing	0	4	
Stage			
III	54 (15.7)	12 (7.8)	
IV	288 (84)	141 (92.2)	**.04**
Missing	0	0	
PD-L1			
<1%	0	62 (40.5)	
1-49%	16 (4.7)	22 (14.4)	
>=50%	326 (95.0)	4 (2.6)	**<.0001**
Missing	0	65	
LDH			
>ULN	66 (29.3)	48 (41)	
Normal	159 (70.7)	69 (59)	**.029**
Missing	117	36	
Albumin			
<LLN	42 (15.6)	21 (16.9)	
Normal	227 (84.4)	103 (83.1)	.74
Missing	74	29	
Haemoglobin			
<LLN	58 (19.3)	45 (32.9)	
Normal	243 (80.7)	92 (67.1)	**.002**
Missing	42	16	
Platelets			
>ULN	76 (25.3)	32 (23.5)	
Normal	224 (74.7)	104 (76.4)	.69
Missing	42	17	
Leukocytes			
<LLN	68 (23)	39 (28.9)	
Normal	228 (77)	96 (71.1)	.18
Missing	46	18	
Neutrophil Lymphocyte Ratio			
>3	123 (41.4)	58 (42.7)	

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Table 1 (*continued*)

	Training Cohort n=342	Test Cohort n=153	*P* Value
<3	174 (58.6)	78 (57.3)	.81
Missing	45	17	
Calcium			
Normal	168 (69.7)	83 (70.9)	
>ULN	73 (30.3)	34 (29.1)	.81
Missing	101	36	
Liver Metastases			
Present	58 (16.9)	37 (24.2)	.13
Missing	1	0	
Brain Metastases			
Present	45 (13.2)	21 (13.77)	.63
Missing	2	0	
Bone Metastases			
Present	90 (26.4)	53 (34)	.17
Missing	1	0	
ICI			
Pembrolizumab	343 (100)	0	
Nivolumab	0	146 (95.4)	
Atezolizumab	0	7 (4.6)	
Missing	0	0	
Mean No. Cycles ICI (Range)	10.5 (1 - 82)	8.9 (1 - 68)	.87

Table 2 Multivariable Cox Regression Analyses of Final Clinical Variables Derived From the Training Cohort (n=342)

Prognostic Variable	Training Cohort (N = 342)	
	HR (95% CI)	*P*-value
ECOG =1	2.83 (1.59-5.03)	<.001
ECOG ≥2	5.55 (3.04 - 10.13)	<.001
dNLR ≥ 3	2.13 (1.60-2.83)	<.001
LDH > ULN	1.68 (1.26-2.24)	<.001

Table 3 Multivariable Cox Regression Analyses of all Examined Candidate Variables From the Training Cohort (n=342)

Prognostic Variable	Training Cohort (n = 342)	
	HR (95% CI)	*P*-value
ECOG =1	2.42 (1.33, 4.40)	.004
ECOG ≥2	4.50 (2.38, 8.48)	<.001
dNLR ≥ 3	2.00 (1.46, 2.73)	<.001
LDH > ULN	1.46 (1.03, 2.06)	.036
Male sex	1.23 (0.90, 1.69)	.19
Autoimmune Condition at baseline	1.25 (0.88, 1.79)	.21
Age at ICI ≥ 70	1.06 (0.78, 1.43)	.72
Lung metastasis	1.29 (0.94, 1.78)	.11
Liver metastasis	1.18 (0.82, 1.71)	.37
Bone metastasis	1.16 (0.84, 1.62)	.37
Brain metastasis	1.15 (0.74, 1.79)	.52
Adrenal metastasis	1.76 (1.17, 2.66)	.007
Other sites of metastases	1.67 (1.21, 2.31)	.002
BMI >=30	1.47 (0.99, 2.18)	.054
Hemoglobulin < LLN	1.38 (0.98, 1.93)	.06
Thrombocytosis	0.80 (0.55, 1.16)	.24
Corrected calcium > 2.6	0.97 (0.65, 1.45)	.89
Albumin < LLN	1.23 (0.87, 1.75)	.24
Creatinine > 120 umol/L	1.50 (0.91, 2.47)	.12
Smoking history	0.88 (0.51, 1.54)	.66

Abbreviations: ICI = Immune checkpoint inhibitor; LLN = lower limit of normal.

Identifying Prognostic Variables

The median follow-up time in the training cohort was 21 months (95% CI 19.6 - 22.9).

One clinical (ECOG) and 2 laboratory (derived neutrophil to lymphocyte ratio [dNLR] ≥ 3 and lactate dehydrogenase [LDH] ≥ ULN) variables were included in the final multivariable model, based on LASSO Cox regression and independent adverse association with OS, Table 2. The 20 candidate baseline candidate clinical and laboratory variables examined are outlined in Table 3.

Lung Immune Therapy Evaluation (LITE)- Risk

Figure 1A outlines the negative prognostic relationship seen with an increasing risk score in the training cohort.

Model validation indicated that 3-, 4-, and 5-factor models had similar optimism-corrected performance, while the 3-factor model displayed the best performance in the training cohort (Tables 5 & 6). Therefore, we developed a risk score-based prognostic model based on these 3 baseline variables. The presence of each variable

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Figure 1 (A). Kaplan Meier Overall Survival curve for patients in the training cohort, parsed by individual risk score. (B). Kaplan Meier Overall Survival curve for patients in the training cohort, parsed by a 3 risk group model (favorable, intermediate and poor risk). (C). Kaplan Meier Overall Survival curve for patients in the test cohort, parsed by a 3 risk group model (favorable, intermediate and poor risk).

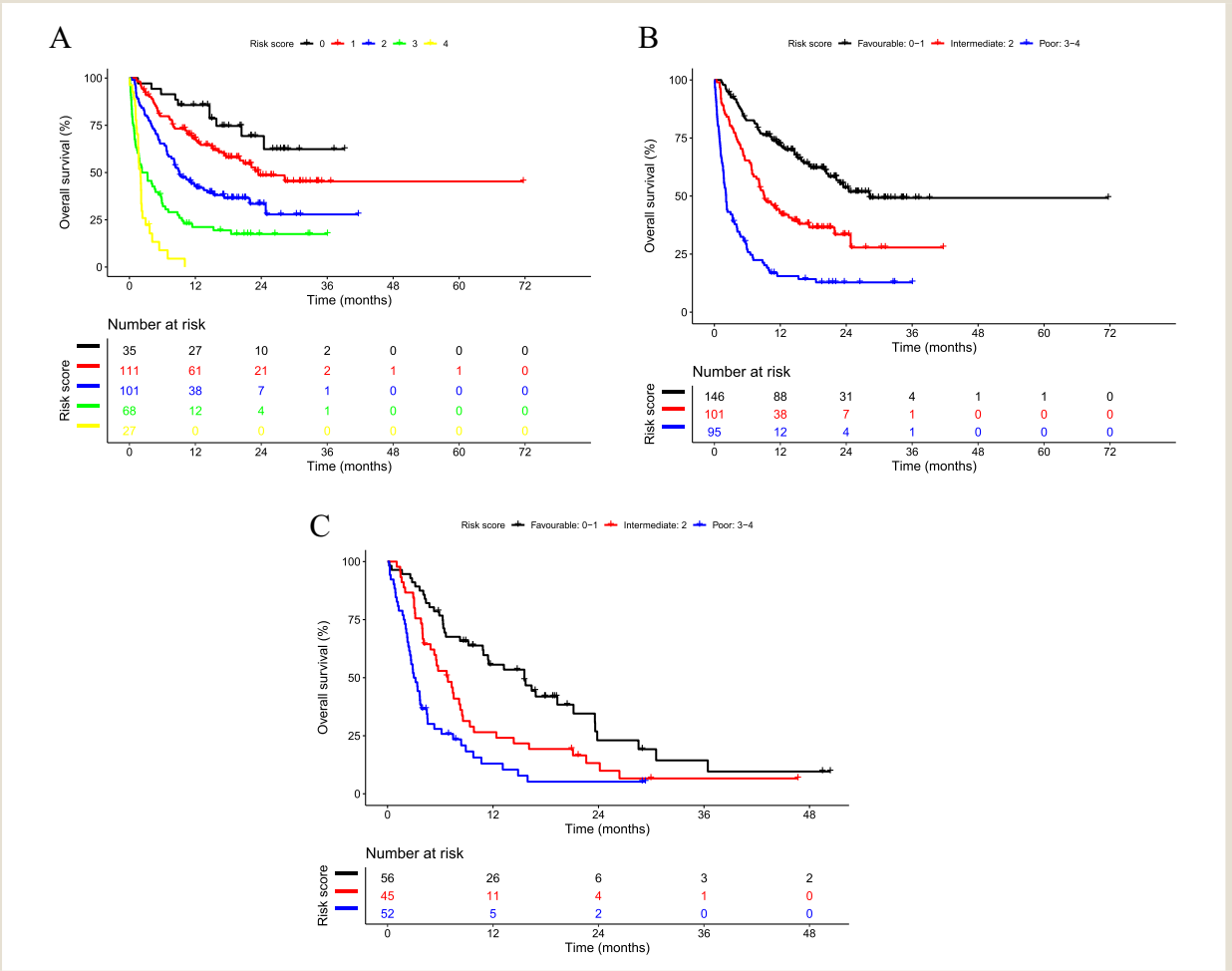

Table 4 Overall Survival Outcomes and Performance of the Final Prognostic Model in Both the Training and Test Cohorts

LITE-Risk Group	HR (95% CI)	mOS (95% CI)	% 1-y OS (95% CI)	% 2-y OS (95% CI)	C-statistic (SE)
			Training Cohort (1L)		**0.702 (0.017)**
Favorable (n=146)	*ref*	28.3 (20.8 - NE)	72.4 (65.3 - 80.2)	53.6 (44.7 - 64.3)	
Intermediate (n=101)	2.08 (1.46 - 2.97)	9.1 (7.1 - 15.3)	43.0 (34.3 - 54.0)	33.4 (24.3 - 46.0)	
Poor (n=95)	5.21 (3.69 - 7.34)	2.1 (1.7 - 3.7)	15.5 (9.6 - 25.2)	12.8 (7.4 - 22.2)	
			Test Cohort (2L)		0.664 (0.024)
Favorable (n=56)	*ref*	15.6 (10.9 - 23.6)	55.6 (43.7 - 70.7)	23.0 (12.3 - 43.2)	
Intermediate (n=45)	1.82 (1.16 - 2.86)	6.9 (4.9 - 8.6)	26.5 (16.1 - 43.8)	13.2 (5.9 - 29.9)	
Poor (n=52)	3.40 (2.18 - 5.29)	3.1 (2.5 - 4.5)	13.0 (6.0 - 28.2)	5.2 (1.4 - 19.6)	

received a score of 1, except for ECOG, in which patients with ECOG ≥ 2 received a score of 2. After comparing several prognostic groupings, a 3 group approach, termed LITE-risk gave the optimum combination of a high C-statistic, 0.702 (SE 0.017) and meaningful discrimination of patient outcomes (Figure 1B, Table 4, Table 7) with LITE favorable risk (n=146, risk score 0-1) median OS (mOS) 28.3 months (95% CI 20.8 – NE), LITE intermediate risk (n=101, risk score of 2) mOS 9.1 months (95% CI 7.1 - 15.3) and LITE poor risk (n=95, risk score ≥ 3) mOS 2.1 months (95% CI 1.7 - 3.7).

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Table 5 Selected Candidate Variables With LASSO Cox Regression and C-Statistic Alongside Coefficients on a Log Scale.

	Training Cohort (n=342)			
No. of Predictors	**3 Predictor**	**4 Predictor**	**5 Predictor**	**6 Predictor**
C-statistic	0.749	0.740	0.739	0.736
ECOG	0.46	0.48	0.48	0.49
N/L ratio≥ 3.0	0.40	0.42	0.42	0.43
LDH > ULN	0.12	0.15	0.16	0.17
Hemoglobulin < LLN		0.02	0.03	0.04
Adrenal metastasis			0.01	0.04
Albumin < LLN				0.01

Table 6 LASSO Derived C-Indices of the Original Model and the Bootstrap Validation

C-statistic, Estimate (SE or 95%CI)	Imputed Set		
No. of Predictors	**3p**	**4p**	**5p**
Apparent performance			
Original sample (first line)	0.749 (0.018)	0.740 (0.017)	0.739 (0.017)
Test dataset (second line)	0.706 (0.027)	0.700 (0.025)	0.695 (0.024)
Bootstrap validation			
Bootstrap sample	0.749 (0.019)	0.745 (0.018)	0.747 (0.016)
Test set (original sample)	0.741 (0.007)	0.735 (0.006)	0.733 (0.006)
Test dataset (second line)	0.696 (0.015)	0.694 (0.015)	0.691 (0.016)
Optimism	0.008 (0.019)	0.010 (0.018)	0.014 (0.016)
Corrected performance	0.741 (0.695, 0.787)	0.730 (0.687, 0.774)	0.725 (0.685, 0.766)

Compared to the favorable risk group, both intermediate risk (HR 2.08; 95% CI 1.46 - 2.97) and poor risk (HR 5.21; 95% CI 3.69 - 7.34) had a significantly increased risk of death ($P < .001$ for both comparisons).

Model Validation

We undertook internal validation on the training set with 500 random bootstrapped resampled datasets to generate an optimism corrected C-statistic of 0.694 (95% CI 0.653 - 0.735), implying high discriminatory ability of the model.

The 3-factor model was then externally validated in the 2L test set, Table 4 and Figure 1C outline that the model consistently discriminated survival outcomes of patients. Compared to the favorable risk group, both intermediate risk (HR 1.82; 95% CI 1.16 - 2.86) and poor risk patients (HR 3.40; 95% CI 2.18 - 5.29) had a significantly increased risk of death ($P < .001$ for both comparisons), C-statistic 0.664 (SE 0.024).

Discussion

The findings of this study suggest that a simple and clinically accessible prognostic model can parse patients with advanced NSCLC treated with single-agent ICI into 3 discrete LITE-risk groups with clinically impactful differing OS, LITE intermediate vs favorable risk (HR 2.08; 95% CI 1.46 - 2.97) and poor vs favorable risk (HR 5.21; 95% CI 3.69 - 7.34), c-statistic 0.702. Consistent model performance was seen in the internally validated training and externally validated test cohorts.

The final 3-variable model included baseline patient ECOG performance status, dNLR and LDH; all of which have previously been described as being independent prognosticators of poor OS in advanced NSCLC.[5,8-10,15] Combining patient focused ECOG with known established markers of systemic inflammation such as LDH[8] and an inflammatory tumor microenvironment via dNLR[16] is attractive mechanistically. Although other groups have derived prognostic models in a similar treatment context,[8,9] our work adds value by providing external validation in a patient cohort treated in the second line setting. Prognostic factors should be intrinsic and not affected by systemic treatment. The clinically meaningful performance of this model in the 1L and 2L settings, which have established differences in baseline characteristics that impact ICI activity, such as level of PD-L1 expression and histology[1] give us confidence in the clinical relevance of LITE-risk groups. Our optimism adjusted c-statistic values in the training and test sets are also comparable to other prognostic models in this context.[9] It is important to note that our statistical approach increased internal validity via bootstrap analysis, which was not undertaken in other similar studies.[8,9] LITE-risk groups are able to provide clinicians new benchmarks for real world OS.

Previous prognostic models in this context such as LIPS-3[9] utilized the same datasets for training and validation, and this single split of datasets have been established to give erroneous estimation of model performance.[17] Our use of bootstrapping for internal validation, LASSO Cox regression to reduce overfitting and reporting of an optimism-corrected C-statistic improves the estimation of the generalization performance of LITE-risk when compared to LIPS-3.[18] We were not able to formally compare our model with LIPS-3 to determine statistical robustness due to the lack of data regarding pretreatment steroids, a LIPS-3 predictor, in our dataset.

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Table 7 Performance and Optimism of Evaluated 3 Factor Risk Score Models

Potential Model	Risk Score	N Patients	N Events	C-Statistic (Original Dataset), Estimate (SE)	Optimism, Mean (SE)	Corrected C-Statistic, Estimate (95% CI)
Binary 1	0–1	146	58	0.651 (0.016)	0.006 (0.014)	0.646 (0.609, 0.682)
	2–4	196	145			
Binary 2	0–2	247	122	0.653 (0.016)	0.006 (0.016)	0.646 (0.607, 0.686)
	3–4	95	81			
Ternary 1	0–1	146	58	0.673 (0.016)	0.008 (0.015)	0.666 (0.628, 0.703)
	2–3	169	119			
	4	27	26			
Ternary 2	0–1	146	58	0.702 (0.017)	0.008 (0.017)	0.694 (0.653, 0.735)
	2	101	64			
	3–4	95	81			
Quaternary	0-1	146	58	0.704 (0.016)	0.008 (0.016)	0.696 (0.655, 0.736)
	2	101	64			
	3	68	55			
	4	27	26			
Individual	0	35	10	0.711 (0.016)	0.008 (0.016)	0.703 (0.664, 0.743)
	1	111	48			
	2	101	64			
	3	68	55			
	4	27	26			

The inferior survival outcomes seen in the LITE-poor risk groups in both the training and validation cohorts, mOS of 2.1 and 3.1 months, respectively are striking. These data are helpful to allow informed conversations about expectations of therapy, and provides further justification for the early involvement of palliative care.[19] It is unclear whether these patients would benefit from treatment intensification with chemo-immunotherapy.

Limitations

The retrospective nature of the work, and accrual of all patients from 1 province may limit the generalizability of our results. The lack of a control group, receiving combined chemo-immunotherapy or chemotherapy alone prevents us from assessing any predictive capabilities of LITE-risk. Our focus on overall survival as the primary outcome, and data capture only from time of ICI initiation, means that delineating the benefit of any subsequent lines of chemotherapy (for the 1L training cohort) from the survival gain provided by ICI is difficult.

Due to the limited patient population studied, it is not clear if our prognostic model applies in patients treated with other systemic therapies alone such cytotoxic chemotherapy or in other, earlier disease states amenable to curative intent ICI[20] after definitive chemoradiation. Our use of a 2L cohort as an external validation population may be controversial, due to the known differences in baseline characteristics and survival outcomes compared to an ICI naïve setting and thus prospective validation from larger, international datasets are required. PD-L1 expression is an established predictive biomarker in the 1L[21] and 2L ICI[22,23] contexts. However, in our dataset the rate of PD-L1 expression "missingness" in the test cohort (2L) was 42.4% (65/153), as opposed to 0% in the training cohort (1L), as it is not a public reimbursement payor requirement prior to receipt of 2L therapy, as opposed to 1L therapy. Statistical approaches would be unreliable in this context as the data are not missing at random, making MICE an inappropriate tool, therefore we elected not to evaluate this as a candidate variable. The assessment of LITE-risk in association with PD-L1 expression should be evaluated prospectively to outline the prognostic/and or predictive value of this model.

A prognostic variable used, LDH was missing data in 34% of patients. However, when examining the impact of this missing data on variable selection, it is likely that LDH is missing at random, and so MICE is an appropriate tool.[24] Other modelling approaches within oncology may achieve a higher discriminatory ability, for example nomograms,[25] however we intentionally focused on a LITE-risk score that was easy to derive, utilizing commonly used a priori cut-offs. This provides parsimony and the ease of use should not be understated were this to be incorporated into practice. Statistical information and power is commonly lost with categorization in this way, but is common in medicine.

Conclusion

This study describes the derivation and external validation of a simple prognostic model, LITE-risk, utilizing readily accessible clinical data points for patients with advanced NSCLC treated with ICI monotherapy.

Clinical Practice Points

- Question: Can readily available clinical data be used to inform a prognostic scoring model in patients with advanced non-small cell

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lung cancer (NSCLC) treated with immune checkpoint inhibitors (ICI)?

- Findings: In this cohort study of 495 patients with NSCLC, a prognostic scoring system was derived and externally validated. Patients were parsed into 3 discrete risk groups. The final model consisted of the following baseline characteristics: Eastern Oncology Cooperative Group (ECOG) performance status, derived neutrophil to lymphocyte ratio (dNLR) and lactate dehydrogenase (LDH).
- Meaning: A simple prognostic scoring tool utilizing accessible clinical data can discriminate survival outcomes in patients with advanced NSCLC treated with single-agent ICI.

Credit Author Statements

Dr. Vishal Navani had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis. All information and material in the manuscript are original. Dr Heng reported receiving grants from Pfizer, Novartis, Bristol-Myers Squibb, Ipsen, Merck, and Eisai outside the submitted work. Dr Navani reports personal consulting fees from Kwoya Kirin, Novotech PTY, Pfizer, Astra Zeneca, EMD Serono and IPSOS.

Data Availability

Data analysis and statistical code utilized can be made available on reasonable request.

Acknowledgment

A provinical statewide Alberta ethics (Health Research Ethics Board of Alberta) has provided overseeing ethics approval for this study (HREBA.CC-19-0380).

Disclosure

The authors have stated that they have no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cllc.2022.12.014.

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