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Hypoalbuminemia can strongly predict severe acute lung morbidity in locally advanced non-small cell lung cancer

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Background & Aim

- The mainstay of locally advanced NSCLC is concurrent chemoradiation (CCRT)
- Meta-analysis: Severe and fatal radiation pneumonitis 3.62% - 7.85%[1]
- Pneumonia is also a common event:
  Grade ≥ 3 pneumonia → 4% in PACIFIC trial[2]
- Distinguishing radiation pneumonitis and infectious pneumonia is often hard in practice
- **Aim**
  → To investigate the clinical effects and predictive factors of severe acute lung morbidity (SALM) after CCRT for locally advanced NSCLC

[1] Kuang Y et al. *Lung Cancer* 2022.
[2] Angonia SJ et al. *N Engl J Med* 2017.

Methods

- Retrospective study
- Inclusion criteria
  - Definitive CCRT for locally advanced NSCLC (inoperable stage II-III)
  - January 2012 – August 2020
- Exclusion criteria
  - Underwent neoadjuvant chemotherapy
- 317 patients were enrolled

Methods

- SALM
  → Admission or emergency department visit for treatment of lung complication within 6 months from initiation of CCRT
- Analyzed covariates → total 28
  - Baseline patient characteristics
  - Pulmonary function test
  - Dosimetric features of RT
  - Laboratory test results during CCRT

Patient characteristics

- Median follow-up 24 months (range, 1-100 months)

Characteristics	Without severe acute lung morbidity (N = 264)	With severe acute lung morbidity (N = 53)	P-value
Age at diagnosis (median, years)	65 (range, 40-94)	70 (range, 48-82)	0.001
Sex			0.723
Male	43 (16.3%)	7 (13.2%)	
Female	221 (83.7%)	46 (86.8%)	
ECOG performance status			1.000
0-1	261 (98.9%)	52 (98.1%)	
2	3 (1.1%)	1 (1.9%)	
Smoking status			0.051
Current smoker	111 (42.0%)	16 (30.2%)	
Ex-smoker	97 (36.7%)	29 (54.7%)	
Non-smoker	56 (21.2%)	8 (15.1%)	
Histology			0.420
Adenocarcinoma	119 (45.1%)	22 (41.5%)	
Squamous cell carcinoma	118 (44.7%)	28 (52.8%)	
Others	27 (10.2%)	3 (5.7%)	
Clinical stage (AJCC 8th)			0.049
IIA/B	13 (4.0%)	0 (0.0%)	
IIIA	141 (53.4%)	33 (62.3%)	
IIIB	90 (34.1%)	12 (22.6%)	
IIIC	20 (7.6%)	8 (15.1%)	
FEV1 (median, L)	2.32 (range, 0.98-4.14)	2.17 (range, 1.02-3.32)	0.052
FVC (median, L)	3.40 (range, 1.32-5.47)	3.22 (range, 1.87-4.68)	0.023
FEV1/FVC (%, median)	70% (range, 35-87%)	70% (range, 49-91%)	0.605

Characteristics	Without severe acute lung morbidity (N = 264)	With severe acute lung morbidity (N = 53)	P-value
DLCO (median, ml/min/mmHg)	15.9 (range, 6.7-29.6)	12.5 (range, 5.6-22.8)	< 0.001
Chemotherapy regimen			0.720
Carboplatin and paclitaxel	187 (70.8%)	41 (77.4%)	
Docetaxel and cisplatin	68 (25.8%)	11 (20.8%)	
Weekly cisplatin	3 (1.1%)	0 (0.0%)	
Others	6 (2.3%)	1 (1.9%)	
Radiation therapy technique			0.037
3D-CRT	134 (50.8%)	18 (34.0%)	
VMAT	130 (49.2%)	35 (66.0%)	
Consolidative durvalumab	20 (7.6%)	3 (5.7%)	0.841
EQD2 of prescribed dose (median, Gy)	60.0 (range, 44.0-93.3)	60.0 (range, 40.0-81.3)	0.054
Bilateral lung mean dose (median, Gy)	15.76 (range, 4.33-24.05)	18.07 (range, 4.78-22.75)	< 0.001
Bilateral lung V5 (median)	57.7% (range, 16.7-96.6%)	72.8% (range, 27.9-100.0%)	< 0.001
Bilateral lung V20 (median)	25.5% (range, 5.8-44.1%)	32.3% (range, 4.7-41.5%)	< 0.001
Bilateral lung volume (median, cm^3)	3183 (range, 1336-5960)	2876 (range, 1699-4680)	0.196
Heart mean dose (median, Gy)	10.17 (range, 0.0-39.63)	16.89 (range, 0.10-41.23)	< 0.001
Size of PTV (median, cm^3)	350 (range, 63-1188)	413 (range, 137-1324)	0.026
RT duration (median, days)	44 (range, 16-88)	44 (range, 20-56)	0.452

Adverse events

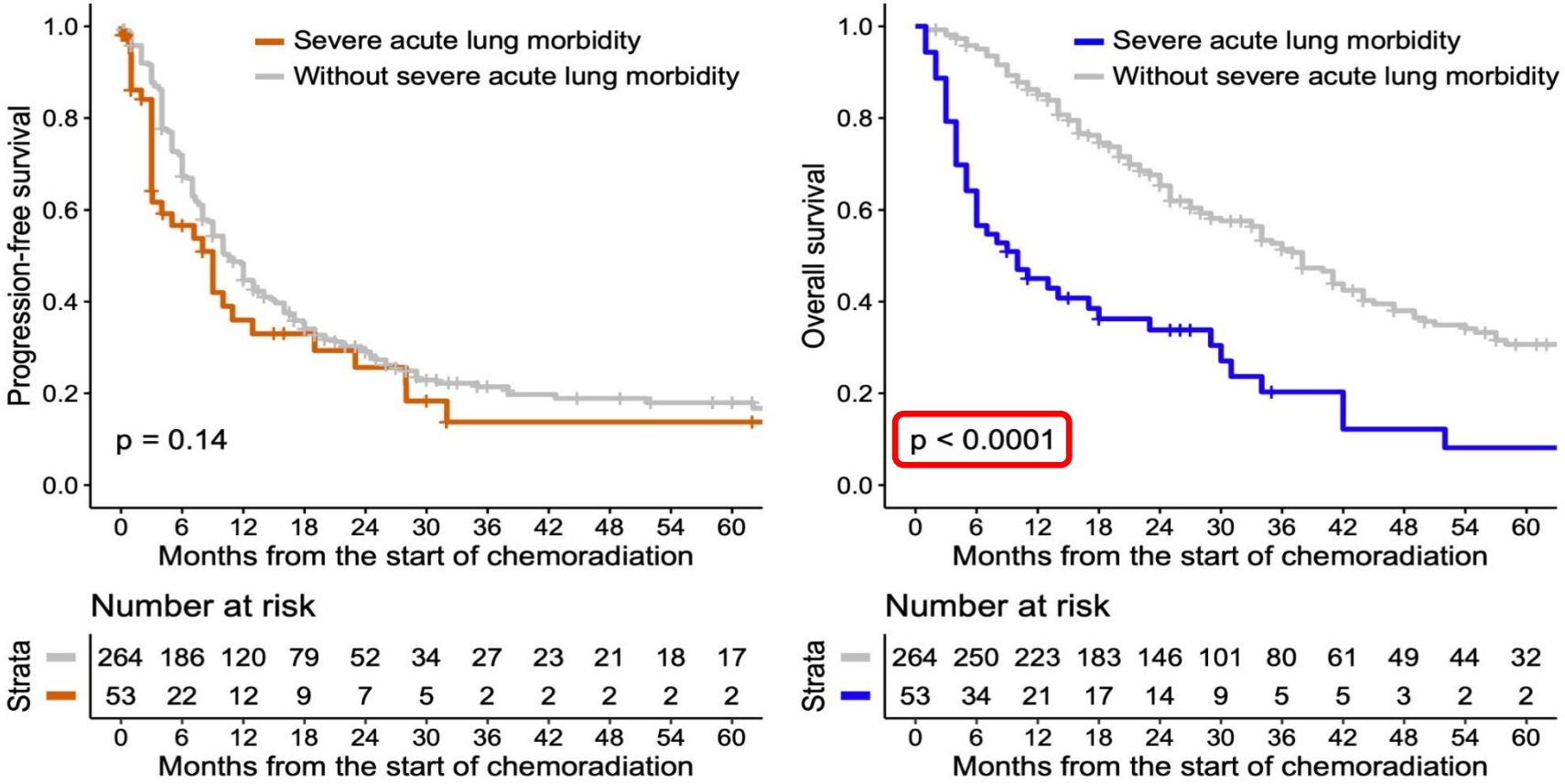
- SALM was reported in 53 (16.7%)
  - 18 (34.0%) – RT pneumonitis
  - 18 (34.0%) – Infectious pneumonia
  - 17 (32.1%) – Superimposed or undistinguishable
- 13 (4.1%) patients died from SALM
- CTCAE grading

Grade	Symptomatic RT pneumonitis	Pneumonia	Anemia	Leukopenia	Neutropenia	Lympho-cytopenia	Thrombo-cytopenia	Hypoalbumi-nemia
1	- *	- †	215 (68.0%)	90 (28.5%)	37 (11.7%)	5 (1.6%)	78 (24.7%)	33 (10.4%)
2	63 (19.9%)	13 (4.1%)	77 (24.4%)	107 (33.9%)	59 (18.7%)	48 (15.1%)	10 (3.2%)	32 (10.1%)
3	10 (3.2%)	16 (5.0%)	0 (0.0%)	56 (17.7%)	35 (11.1%)	179 (56.5%)	5 (1.6%)	2 (0.6%)
4	3 (0.9%)	4 (1.3%)	0 (0.0%)	7 (2.2%)	4 (1.3%)	82 (25.9%)	1 (0.3%)	0 (0.0%)
5	9 (2.8%)	10 (3.2%)	0 (0.0%)	- †	- †	- †	- †	0 (0.0%)

* Grade 1 radiation pneumonitis is asymptomatic.

† The event was not defined in CTCAE v5.0.

Association of SALM and Prognosis



- SALM was associated with **poor overall survival** but not with progression-free survival

Prediction of SALM

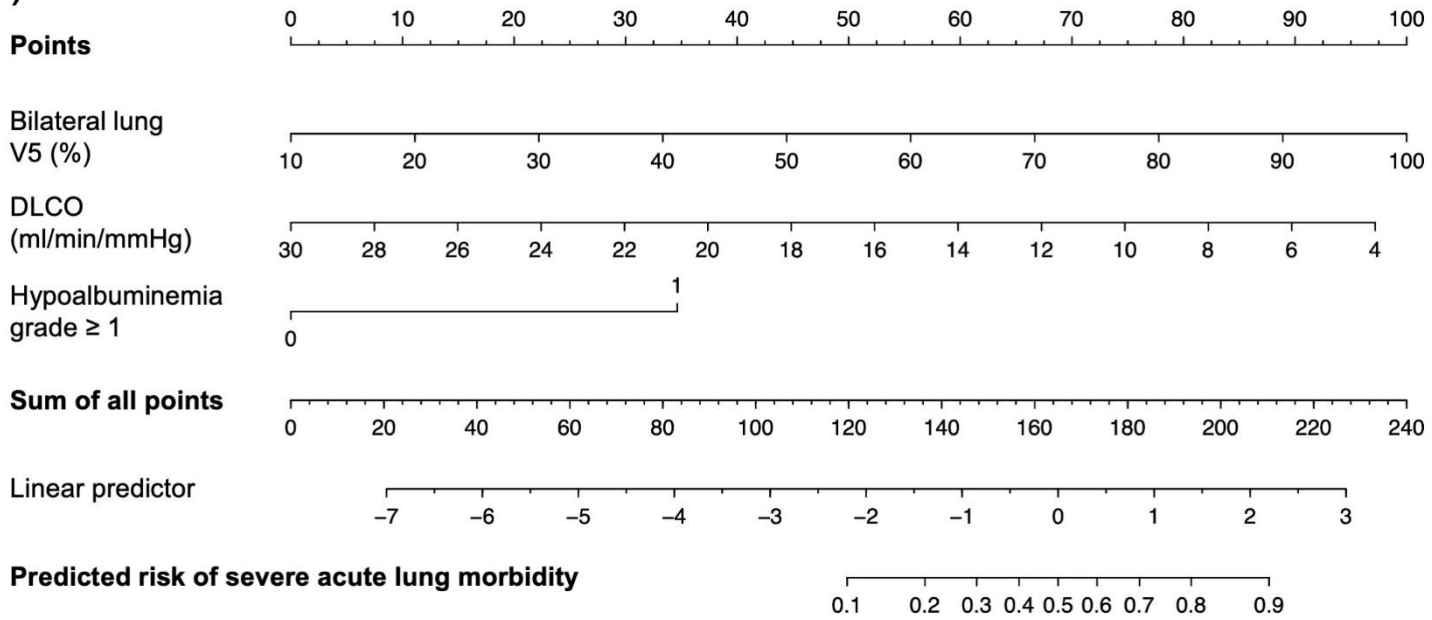
Characteristics (comparison vs. reference)	Univariate analysis			Multivariate analysis*		
	OR	95% CI	Adjusted P-value	OR	95% CI	P-value
Age at diagnosis (continuous, per a year)	1.050	1.015-1.088	0.019	1.007	0.959-1.056	0.790
Sex (female vs. male)	0.782	0.306-1.751	0.767	-	-	-
Amount of smoking (continuous, per pack-year)	1.013	1.001-1.026	0.083	1.010	0.992-1.028	0.248
Body mass index (continuous, per kg/m^2)	0.985	0.893-1.083	0.834	-	-	-
Histology (others vs. adenocarcinoma)	1.156	0.639-2.123	0.771	-	-	-
FEV1 (continuous, L)	0.660	0.401-1.061	0.162	-	-	-
FEV1, percentage predicted value (continuous, per 10%)	0.999	0.862-1.160	0.994	-	-	-
FVC (continuous, per L)	0.628	0.415-0.936	0.062	0.741	0.398-1.346	0.333
FVC, percentage predicted value (continuous, per 10%)	0.916	0.757-1.110	0.545	-	-	-
FEV1/FVC (%, continuous, per 10%)	1.075	0.821-1.427	0.769	-	-	-
DLCO (continuous, per ml/min/mmHg)	0.801	0.729-0.872	< 0.001	0.855	0.743-0.974	0.022
DLCO, percentage predicted value (continuous, per 10%)	0.662	0.544-0.793	< 0.001	-*	-*	-*
Regimen of chemotherapy (others vs. carboplatin + paclitaxel)	0.711	0.341-1.388	0.523	-	-	-
RT technique (3D-CRT vs. VMAT)	0.499	0.264-0.915	0.064	0.671	0.294-1.498	0.333

Characteristics (comparison vs. reference)	Univariate analysis			Multivariate analysis*		
	OR	95% CI	Adjusted P-value	OR	95% CI	P-value
EQD2 of prescribed dose (continuous, per Gy)	0.942	0.885-0.999	0.098	0.949	0.874-1.021	0.184
Bilateral lung mean dose (continuous, per Gy)	1.178	1.081-1.293	0.001	-	-	-
Bilateral lung V5 (continuous, per 10%)	1.692	1.386-2.095	< 0.001	1.872	1.336-2.699	< 0.001
Bilateral lung V20 (continuous, per 10%)	2.358	1.548-3.705	0.001	-	-	-
Bilateral lung volume (continuous, per 100 cm^3)	0.976	0.939-1.012	0.323	-	-	-
Heart mean dose (continuous, per Gy)	1.065	1.031-1.102	0.001	0.969	0.918-1.020	0.231
Size of PTV (continuous, per 100 cm^3)	1.175	1.039-1.327	0.027	0.938	0.781-1.118	0.479
Duration of RT (continuous, per day)	0.981	0.934-1.030	0.630	-	-	-
Anemia grade ≥ 2 (yes vs. no)	3.084	1.645-5.754	0.001	1.357	0.575-3.135	0.478
Leukopenia grade ≥ 2 (yes vs. no)	1.002	0.552-1.830	0.994	-	-	-
Neutropenia grade ≥ 2 (yes vs. no)	1.097	0.570-2.047	0.834	-	-	-
Lymphocytopenia grade ≥ 3 (yes vs. no)	3.005	1.159-10.27	0.085	1.067	0.323-4.311	0.920
Thrombocytopenia grade ≥ 2 (yes vs. no)	0.714	0.110-2.663	0.773	-	-	-
Hypoalbuminemia grade ≥ 1 (yes vs. no)	7.186	3.806-13.77	< 0.001	5.670	2.487-13.40	< 0.001

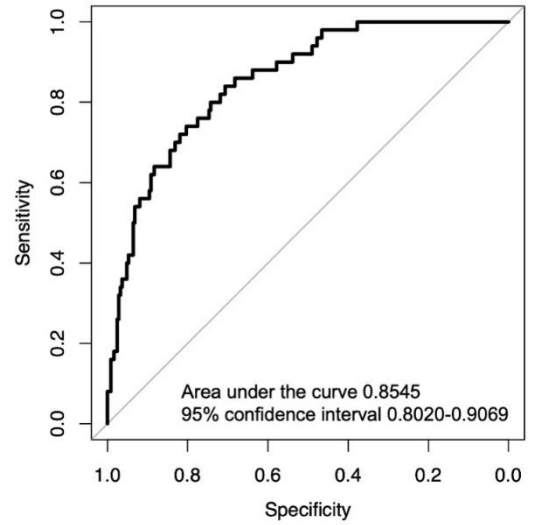
* Removed from multivariate analysis due to collinearity

Nomogram

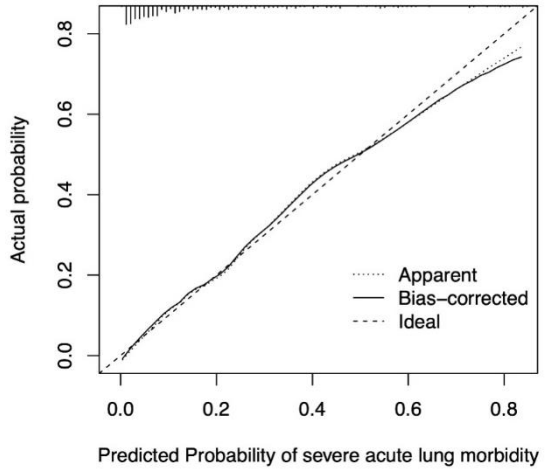
(A)



(B)



(C)



(A) Nomogram for predicting the probability of SALM
(B) Receiver operating characteristic curve
Area under the curve **0.8545**, 95% CI 0.8020-0.9069
(C) Calibration plot with bootstrapping of 100 repetitions for the nomogram

Conclusion

- We defined SALM based on the event of admission or emergency department visit with treatment of lung adverse events of CCRT
- SALM was significantly associated with overall survival but not with progression-free survival
- Lower baseline DLCO, higher bilateral lung V5, and grade ≥ 1 hypoalbuminemia during CCRT were associated with SALM