Nomograms Predict Overall Survival for Patients with Small-Cell Lung Cancer Incorporating Pretreatment Peripheral Blood Markers

Dong Xie, MD, PhD,† Randolph Marks, MD,‡ Mingrui Zhang, PhD,† Gening Jiang, MD,* Aminah Jatoi, MD,‡ Yolanda I. Garces, MD,§ Aaron Mansfield, MD,‡ Julian Molina, MD,‡ and Ping Yang, MD, PhD†*

Background: We sought to build prognostic nomograms and identify novel prognostic factors in small-cell lung cancer (SCLC) incorporating both clinical data and peripheral blood markers.

Methods: We analyzed 938 patients with SCLC (555 extensive stage SCLC [ES-SCLC] and 383 limited stage SCLC [LS-SCLC]) diagnosed between 1997 and 2012 from a single institution. We investigated the prognostic value of pretreatment neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, red cell distribution width, hemoglobin, and other clinicopathological factors. Cox proportional hazards models determined the effects of multiple factors on overall survival (OS). Two nomograms were developed to predict median survival and 6- and 12-month OS for ES-SCLC, and 1- and 2-year OS for LS-SCLC.

Results: In ES-SCLC, the multivariate Cox model identified neutrophil to lymphocyte ratio and red cell distribution width as significant prognostic factors for OS independent of age, Eastern Cooperative Oncology Group performance score, chest radiation, chemotherapy, liver metastases, and numbers of metastatic sites. In LS-SCLC, significant prognostic variables included platelet to lymphocyte ratio, age, smoking cessation, chest radiation, chemotherapy, surgery, and prophylactic cranial irradiation. The two nomograms show good accuracy in predicting OS, with a concordance index of 0.73 in both ES- and LS-SCLC.

Conclusion: The two nomograms incorporating hematological markers could more accurately predict individualized survival probability of SCLC than the existing models.

Key Words: Small-cell lung cancer, Survival, Prediction model, Nomogram, Neutrophil to lymphocyte ratio, Hematological markers.

(*J Thorac Oncol.* 2015;10: 1213–1220)

Approximately 14% of all lung cancer cases (more than 30,000 patients) in the US have small-cell lung cancer (SCLC).[1,2] SCLC treatment remains unsatisfying, as minimal breakthroughs have occurred in the past decade. Despite high initial responses to therapy, most patients die from recurrent disease, and the median survival after diagnosis is estimated to be 8–20 months. To better predict the SCLC patients' outcomes, various prognostic factors and models have been investigated, such as age, gender, performance score (PS), serum neuron-specific enolase (NSE), serum lactate dehydrogenase, the Spain prognostic index,[3] and the Manchester Score.[4] The development of novel prognostic factors and models will enable a better treatment stratification for patients with SCLC.

Statistical prediction models are widely used for predicting cancer outcomes. Among those, the nomogram is a graphical presentation of the results from a statistical model, which utilizes combined prognostic factors in predicting outcome for a given patient. Individualized estimation of survival among patients with cancer could be useful for counseling patients in making treatment decisions and optimizing therapeutic approaches. However, to the best of our knowledge, no nomogram has been reported for SCLC.

Inflammation is a known critical component of cancer progression.[5] Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) in peripheral blood have been proposed as reliable indicators of the host's inflammatory status; they have been identified as both prognostic and predictive biomarkers in many types of cancer including non–small-cell lung cancer.[6–8] Recently, two studies have shown that elevated red cell distribution width (RDW) level is also a marker of poor prognosis

*Department of Thoracic Surgery, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, People's Republic of China; †Division of Epidemiology, Department of Health Sciences Research, Mayo Clinic College of Medicine, Rochester, Minnesota, ‡Division of Medical Oncology, and §Department of Radiation Oncology, Mayo Clinic, Rochester, Minnesota.

The work was supported by the USA National Institutes of Health Grants (R03 CA77118, R01 CA80127, R01 CA84354, and R01CA115857) and Mayo Clinic Foundation, Foundation for Youths of Shanghai Municipal Health Bureau (2012093), and Shanghai Hospital Development Center Grant (Grant No. shdc12012111).

Disclosure: The authors declare no conflict of interest.

Address for correspondence: Ping Yang, MD, PhD, Department of Health Sciences Research, Mayo Clinic, 200 First Street SW, Rochester, MN 55905. E-mail:yang.ping@mayo.edu

DOI: 10.1097/JTO.0000000000000585

ISSN: 1556-0864/15/1008-1213

TABLE 1. Characteristics of All SCLC by Stage

Characteristic	ES-SCLC (*n* = 555) No. (%)	LS-SCLC (*n* = 383) No. (%)	*p*
Age at diagnosis			0.9499
Mean (SD)	66.7 (10.3)	66.7 (10.0)	
Gender			0.0032
Female	237 (42.7%)	201 (52.5%)	
Male	318 (57.3%)	182 (47.5%)	
Smoking status			0.3384
Never	12 (2.2%)	5 (1.3%)	
Former	200 (36.0%)	151 (39.4%)	
Current	343 (61.8%)	227 (59.3%)	
Pack-year			0.0025
Missing	49 (0.0%)	21 (0.0%)	
0–19	47 (9.3%)	16 (4.4%)	
20–39	132 (26.1%)	74 (20.4%)	
40–59	138 (27.3%)	127 (35.1%)	
>60	189 (37.4%)	145 (40.1%)	
Smoking cessation			0.0693
Quit or never smoker	375 (67.6%)	280 (73.1%)	
Never quit	180 (32.4%)	103 (26.9%)	
ECOG performance status			<0.0001
<2	399 (71.9%)	331 (86.4%)	
≥2	156 (28.1%)	52 (13.6%)	
BMI			0.4278
Missing	14 (0.0%)	7 (0.0%)	
<25	187 (34.6%)	142 (37.8%)	
25–30	230 (42.5%)	144 (38.3%)	
>30	124 (22.9%)	90 (23.9%)	
Therapy			<0.0001
No treatment	114 (20.5%)	19 (5.0%)	
Surgery with adjuvant therapy	6 (1.1%)	52 (13.6%)	
Chemotherapy or chest radiation only	292 (52.6%)	75 (19.6%)	
Chemotherapy plus chest radiation	143 (25.8%)	237 (61.9%)	
Chemotherapy			<0.0001
No	125 (22.5%)	36 (9.4%)	
Yes	430 (77.5%)	347 (90.6%)	
Chest radiation			<0.0001
No	399 (71.9%)	126 (32.9%)	
Yes	156 (28.1%)	257 (67.1%)	
PCI			<0.0001
No	536 (96.6%)	293 (76.5%)	
Yes	19 (3.4%)	90 (23.5%)	
Platinum agent			0.0042
No chemotherapy	125 (0.0%)	36 (0.0%)	
No	41 (9.5%)	13 (3.7%)	
Yes	376 (87.4%)	318 (91.6%)	
Unknown	13 (3.0%)	16 (4.6%)	
Chemotherapy-agent combination			0.0022
No chemotherapy	125 (0.0%)	36 (0.0%)	
VP16 + CDDP/CBP	351 (81.6%)	305 (87.9%)	
Other combination	66 (15.3%)	26 (7.5%)	
Unknown	13 (3.0%)	16 (4.6%)	

(*Continued*)