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A Model to Predict the Use of Surgical Resection for Advanced-Stage Non-Small Cell Lung Cancer Patients

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Background. **For advanced-stage non-small cell lung cancer, chemotherapy and chemoradiotherapy are the primary treatments. Although surgical intervention in these patients is associated with improved survival, the effect of selection bias is poorly defined. Our objective was to characterize selection bias and identify potential surgical candidates by constructing a Surgical Selection Score (SSS).**

Methods. **Patients with clinical stage IIIA, IIIB, or IV non-small cell lung cancer were identified in the National Cancer Data Base from 1998 to 2012. Logistic regression was used to develop the SSS based on clinical characteristics. Estimated area under the receiver operating characteristic curve was used to assess discrimination performance of the SSS. Kaplan-Meier analysis was used to compare patients with similar SSSs.**

Results. **We identified 300,572 patients with stage IIIA, IIIB, or IV non-small cell lung cancer without missing data; 6% (18,701) underwent surgical intervention. The surgical cohort was 57% stage IIIA (n = 10,650), 19% stage IIIB (n = 3,483), and 24% stage IV (n = 4,568). The areas under the receiver operating characteristic curve from the best-fit logistic regression model in the training and validation sets were not significantly different, at 0.83 (95% confidence interval, 0.82 to 0.83) and 0.83 (95% confidence interval, 0.82 to 0.83). The range of SSS is 43 to 1,141. As expected, SSS was a good predictor of survival. Within each quartile of SSS, patients in the surgical group had significantly longer survival than nonsurgical patients ($p < 0.001$).**

Conclusions. **A prediction model for selection of patients for surgical intervention was created. Once validated and prospectively tested, this model may be used to identify patients who may benefit from surgical intervention.**

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For patients with advanced-stage (stages IIIA, IIIB, and IV) non-small cell lung cancer (NSCLC), 5-year survival remains very poor despite the introduction of new systemic therapies [1]. Treatment approaches for these patients are very heterogeneous, and a small proportion of these patients undergo surgical intervention alone or combined with other modalities [1]. Overall, in the setting of poor survival outcomes as well as the potential morbidity of an invasive operation, curative-intent treatments, such as surgical resection, are not the primary focus of multimodality therapy because the goals of care remain disease control and palliation [2].

However, the inclusion of surgical intervention into the treatment strategy for advanced-stage NSCLC has been reproducibly associated with improvements in survival [3–8]. Using data from population-based and institutional databases, we and others have demonstrated significantly longer cancer-specific and overall survival in advanced NSCLC patients treated with surgical intervention (alone or in combination) compared with nonsurgical modalities, including chemoradiotherapy, chemotherapy alone, radiotherapy alone, and no treatment ($p < 0.001$) [3–6]. Similarly, in a propensity-matched analysis using data from the National Cancer Data Base (NCDB), stage IIIB patients treated with chemotherapy, radiotherapy, and surgical resection had a median survival of 28.9 months compared with 17.2 months for patients treated with chemoradiotherapy without surgical intervention ($p < 0.001$) [4].

A routine criticism of these analyses is that selection bias (even with advanced statistical techniques such as propensity matching) remains an important

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confounding factor potentially accounting for superior survival outcomes observed for surgical patients [4, 5, 9]. This selection bias may reflect the influence of treatment-related variables that are not independently associated with the outcome variable of interest. Yet, despite an understanding of surgical selection bias as a concept, the measurable effect of surgical selection bias on outcomes has been difficult to quantify, partly because of limited data on clinical and pathologic characteristics related to selection for surgical intervention, particularly in advanced-stage NSCLC. Our objective was to quantify the factors influencing selection of advanced-stage NSCLC patients for operations by generating a predictive model, the Surgical Selection Score (SSS). We hypothesized that the SSS would be independently associated with increased overall survival (OS).

Patients and Methods

This study received a determination letter from the University of California, Davis Institutional Review Board. We queried the NCDB for cases of NSCLC proven on biopsy specimens from 1998 to 2012. The NCDB is a joint program of the Commission on Cancer and the American Cancer Society. Data from the NCDB represent 1,500 Commission on Cancer–accredited facilities including more than 70% of all newly diagnosed cancer cases in the United States. These data are used to track treatments and outcomes as well as provide quality-related performance measures [10].

Patients with stage IIIA, IIIB, and IV NSCLC with histologic data available were included. The study cohort is summarized in Figure 1. Standard patient, tumor, and treatment data were extracted and categorized as appropriate. Operations included wedge resection, sublobar resection, lobectomy, bilobectomy, and pneumonectomy. Patient comorbidities were assessed using the Charlson Comorbidity Index, described by Deyo and colleagues [11]. Additional categoric variables examined included clinical tumor group, clinical tumor size, clinical node group, clinical metastases group, histology, age, sex, race, income, education, insurance status, and treatment facility. Age was categorized by percentile (10th, 25th, 50th, 75th, and 90th). Income categories were defined low, less than $38,000; middle, $38,000 to 47,999; and high, more than $48,000. Education categories were defined by the percentage of adults in the patients' zip code who did not graduate from high school: low, 13% or more; middle, 7% to less than 13%; and high, less than 7%. Patients with an additional cancer diagnosis, missing TNM stage group, stage I or II, or missing Charlson-Deyo Index or other demographic data were excluded.

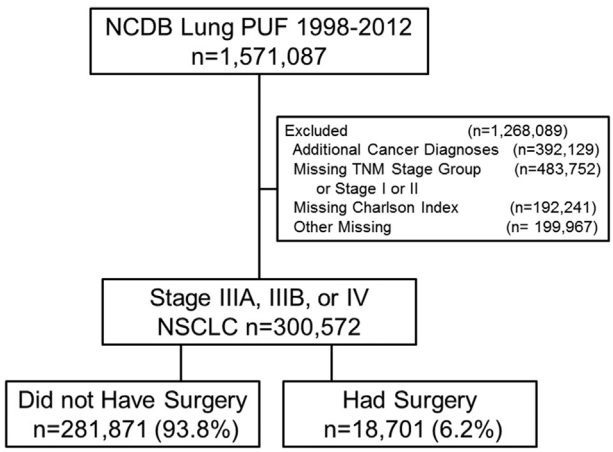

Fig 1. Cohort of stage IIIA, IIIB, and IV patients from the National Cancer Database (NCDB) Participant Use Files (PUF). (NSCLC = non-small cell lung cancer; TNM = tumor-node-metastasis.)

Statistical Analyses

Categorical variables were compared using χ^2 tests to determine differences among the treatment groups (Table 1). Logistic regression was used to create the SSS using models containing increasing numbers of clinical and tumor characteristics, as shown in Figure 2, with the outcome variable representing inclusion of surgical intervention in the treatment regimen [12]. The models were developed in a nested fashion with a simple model initially, and then complexity increased as clinical factors were added. The SSS was developed on a training data set and was validated using a separate validation data set. These training and validation sets were generated using stratified randomization to maintain the proportion of surgical patients in each data set. The entire cohort was split 50/50 into two sets, one for training and one for validation. The ability of each model to predict selection for surgical intervention was assessed and validated by calculating the area under the receiver operating characteristic curve (AUROC) [13]. The equality of the AUROCs from the training and validation sets was compared using the χ^2 test. The final model was determined using the Bayesian information criterion [14].

SSS Creation

The SSS was created by multiplying the logarithm of the odds ratios from the logistic regression model by 100 and adding the total to generate one numeric score for each patient. The probability of undergoing surgical therapy was calculated for the entire cohort and separately by stage. OS functions were estimated using Kaplan-Meier method within treatment groups. Log-rank tests were conducted to examine whether the differences in OS between the treatment groups were statistically significant within quartiles of the SSS. Statistical significance was considered at p values of less than 0.05. Statistical analyses were conducted using SAS 9.4 software (SAS Institute Inc, Cary, NC).

Results

We identified 300,572 patients with specimen-proven stage IIIA, IIIB, or IV NSCLC without missing data, and 18,701 of these patients (6.2%) underwent surgical

Table 1. Surgically Treated Compared With Nonsurgically Treated Patients With Advanced-Stage Non-Small Cell Lung Cancer in the National Cancer Database From 1998 to 2012[a]

Variable	Nonsurgical Patients n = 281,871 (94%) No. (%)	Surgical Patients n = 18,701 (6%) No. (%)
AJCC stage group		
IIIA	47,525 (16.9)	10,650 (56.9)
IIIB	51,603 (18.3)	3,483 (18.6)
IV	182,743 (64.8)	4,568 (24.4)
Histology		
NSCLC	83,826 (29.7)	3,184 (17.0)
Squamous cell carcinoma	75,487 (26.8)	6,171 (33)
Adenocarcinoma	122,558 (43.5)	9,346 (49.9)
Tumor Size		
1a	26,654 (9.5)	2,945 (15.8)
1b	42,176 (14.9)	3,590 (19.2)
2a	91,140 (32.3)	5,735 (30.7)
2b	64,377 (22.8)	3,480 (18.6)
3	57,524 (20.4)	2,951 (15.8)
AJCC T status		
1	36,946 (13.11)	3,875 (20.7)
2	82,382 (29.2)	6,273 (33.5)
3	39,958 (14.2)	3,277 (17.5)
4	97,944 (34.8)	4,458 (23.8)
X	24,641 (8.7)	818 (4.4)
AJCC N status		
0	44,503 (15.8)	4,117 (22)
1	23,775 (8.4)	2,430 (12.9)
2	131,743 (46.7)	10,201 (54.6)
3	50,664 (17.9)	850 (4.6)
X	31,186 (11.1)	1,103 (5.9)
AJCC M status		
0	103,413 (36.7)	14,269 (76.3)
1	133,452 (47.4)	3,530 (18.9)
1A	11,226 (3.9)	331 (1.8)
1B	33,780 (11.9)	571 (3.1)
Charlson-Deyo Index		
0	176,275 (62.5)	10,978 (59.7)
1	73,277 (26)	5,743 (30.8)
2	32,319 (11.5)	1,980 (10.6)
Age, y		
0–52	27,384 (9.7)	2,592 (13.9)
52–59	40,071 (14.2)	3,350 (17.9)
59–67	65,500 (23.2)	5,122 (27.4)
67–75	71,840 (25.5)	4,675 (24.5)
75–81	44,609 (15.8)	2,170 (11.6)
>81	32,467 (11.5)	702 (3.8)
Race		
White	236,598 (83.9)	16,321 (87.3)
Black	36,736 (13)	1,847 (9.9)
Other	8,537 (3.0)	533 (2.9)
Facility type		
Community cancer program	38,445 (13.6)	1,906 (10.2)
Comprehensive community cancer program	160,635 (56.9)	10,022 (53.6)
Academic/research program	82,791 (29.4)	6773 (36.2)
Insurance		
Not insured	13,691 (4.9)	578 (3.1)
Private insurance	84,181 (29.9)	7915 (42.3)
Medicaid	21,701 (7.7)	1,224 (6.6)
Medicare	158,253 (56.1)	8,737 (46.7)
Other government	4,045 (1.4)	247 (1.3)
Income		
Low	59,661 (21.2)	3,478 (18.6)
Middle	76,594 (27.2)	4,757 (25.4)
High	145,616 (51.7)	10,466 (55.9)

[a] Comparisons were by χ^2 test, and all p values were <0.0001.

AJCC = American Joint Committee on Cancer; NSCLC = non-small cell lung cancer.

therapy as part of their treatment regimen (Fig 3). The most common treatment regimens were chemotherapy, radiotherapy, and surgical resection in the surgical cohort and chemotherapy and radiotherapy in the nonsurgical cohort. The surgical cohort was 57% stage IIIA (n = 10,650), 19% stage IIIB (n = 3,483), and 24% stage IV (n = 4,568). As expected, the surgical cohort differed from the nonsurgical cohort for all variables (Table 1).

The AUROCs from the regression models are reported in Table 2. For all of the models, the AUROCs in the training and validation sets were not significantly different. Model 6, which includes histology, tumor size, American Joint Committee on Cancer (AJCC) tumor status, AJCC nodal status, AJCC metastatic status, Charlson-Deyo Index, age, race, facility type, insurance type, and

Models for the Surgical Selection Score

Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Histology	Histology	Histology	Histology	Histology	Histology
	Tumor Size	Tumor Size	Tumor Size	Tumor Size	Tumor Size
	T Status	T Status	T Status	T Status	T Status
	N Status	N Status	N Status	N Status	N Status
	M Status	M Status	M Status	M Status	M Status
		Charlson Index	Charlson Index	Charlson Index	Charlson Index
			Age	Age	Age
				Race	Race
				Facility type	Facility type
				Insurance	Insurance
				Income	Income
				Education*	
				Sex *	

*Fig 2. Logistic regression models used to develop the Surgical Selection Score. *Represents variables without significant predictive ability for selection for surgical intervention. The final model was model 6.*

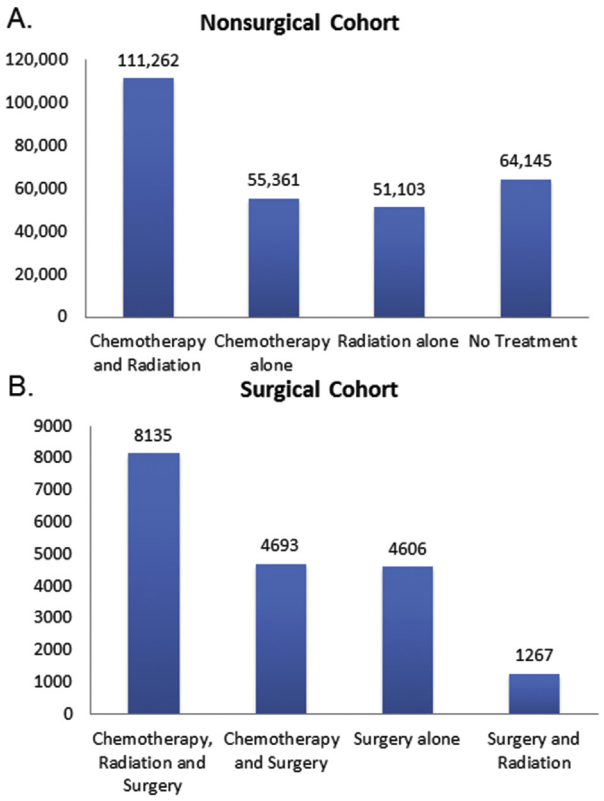

Fig 3. Distribution of treatment regimens in (A) nonsurgically and (B) surgically treated advanced-stage non-small cell lung cancer patients. The nonsurgical cohort is 94% of the total and the surgical cohort is 6%.

income, was chosen as the final model because it had the lowest Bayesian information criterion, indicating that it was the best-performing model (Table 3). Similar results were generated using different random seeds to split the data set into different training and validation sets. The factors that most heavily influenced the decision to select a patient for surgical intervention were AJCC metastatic status, AJCC nodal status, and patient age (Table 3). A sample SSS calculation is shown in Table 3. The SSS is obtained by multiplying the logarithm of the odds ratio for each variable from the logistic regression model by 100 and adding the total, to generate one numeric score for each patient.

Over the entire cohort, the SSS had a bell-shaped distribution (range, 43 to 1,141), and the likelihood of surgical intervention increased sharply in each stage at higher SSS (Fig 4). As expected, patients with stage IIIA disease had a higher SSS and higher probability of surgical intervention (19.5%) than patients with stage IIIB or stage IV disease. In addition, SSS was a good predictor of OS, with patients with the highest SSS surviving longest (Fig 5). Importantly, within each quartile of the SSS, patients in the surgical group also had significantly longer survival than nonsurgical patients ($p < 0.001$). For patients in the lowest quartile of SSS, the median survival time was 9.1 months (95% confidence interval [CI], 8.1 to 10.2 months) in surgical patients vs 4.2 months (95% CI, 4.2 to 4.3 months) in nonsurgical patients ($p < 0.0001$). In the highest quartile of SSS, median survival time was 35.7 months (95% CI, 34.6 to 36.9 months) for surgical patients vs 12.5 months (95% CI, 12.4 to 12.7 months) for nonsurgical patients ($p < 0.0001$).

Comment

This is the first study to develop a quantitative model predictive of selection for surgical treatment for patients with advanced-stage NSCLC. Using detailed clinical variables, readily available at the time of treatment decision making for advanced-stage NSCLC patients, we developed the SSS that predicts the use of surgical intervention for these patients and found evidence that a therapeutic effect of resection remains after accounting for this SSS. Survival for advanced-stage NSCLC is only 4%, and outcomes are generally governed by response to systemic therapy [1]. Yet, the inclusion of surgical therapy into multimodality treatment regimens has been reproducibly associated with improved outcomes [3–8, 15]. A recurrent criticism of these studies is that the observation of improved survival with surgical intervention is attributable to selection bias for patients with favorable characteristics (fewer comorbidities, lower-volume disease) rather the surgical treatment. Yet, it is possible that surgical intervention has a therapeutic effect that remains obscured by the selection bias and that selection bias represents a component part rather than the sum total of the improved outcomes observed in surgically treated patients.

Table 2. Area Under the Receiver Operating Characteristic Curve for Each Logistic Regression Model With Goodness-of-Fit Assessment

Model	TrainSet AUROC	95% CI	ValidSet AUROC	95% CI	χ^2 Test	*p* Value	TrainSet BIC	ValidSet BIC
1	0.77	0.76–0.77	0.77	0.76–0.77	0.14	0.71	61,119	61,043
2	0.81	0.80–0.81	0.81	0.81–0.81	0.36	0.55	58,448	58,522
3	0.81	0.80–0.81	0.81	0.81–0.81	0.35	0.56	58,409	58,470
4	0.82	0.82–0.83	0.83	0.82–0.83	0.14	0.71	56,965	57,053
5	0.83	0.83–0.83	0.83	0.83–0.83	0.06	0.81	56,414	56,471
6	0.83	0.83–0.83	0.83	0.83–0.83	0.05	0.82	56,381	56,436

AUROC = area under receiver operating characteristic curve; BIC = Bayesian information criterion; CI = confidence interval; TrainSet = training set; ValidSet = validation set.

Table 3. Association Between Surgical Treatment and Patient Variables for the Model Creating the Surgical Selection Score

Variable	Odds Ratio (95% CI)	Sample Patient SSS[a]
Clinical T status		
1	2.8 (2.6–3.0)	
2	3.1 (3.0–3.3)	
3	2.4 (2.3–2.6)	
4	Reference	0
X	1.2 (1.1–1.3)	
Tumor Size		
T1a	2.2 (2.1–2.3)	
T1b	1.7 (1.6–1.8)	
T2a	1.2 (1.1–1.2)	
T2b	1.0 (1.0–1.1)	
T3	Reference	0
Clinical N status		
0	14.3 (13.2–15.5)	266
1	11.4 (10.4–12.4)	
2	4.7 (4.4–5.1)	
3	Reference	
X	5.7 (5.2–6.4)	
Clinical M status		
0	15.6 (14.3–17.1)	275
1	1.9 (1.7–2.1)	
1A	2.1 (1.8–2.4)	
1B	Reference	
Histology		
Squamous cell carcinoma	1.8 (1.7–1.9)	
Adenocarcinoma	2.2 (2.1–2.3)	
NSCLC, NOS	Reference	0
Age group, y		
<52	6.1 (5.6–6.7)	181
52–59	4.9 (4.5–5.4)	
59–67	4.1 (3.8–4.5)	
67–75	3.4 (3.1–3.7)	
75–81	2.3 (2.1–2.5)	
>81	Reference	
Charlson-Deyo Index		
0	Reference	0
1	1.3 (1.3–1.3)	
2	1.0 (1.0–1.1)	
Race		
White	1.4 (1.3–1.5)	
Other	1.4 (1.2–1.5)	
Black	Reference	0
Insurance status		
Private	2.0 (1.9–2.2)	
Medicare	1.6 (1.4–1.7)	
Medicaid	1.2 (1.1–1.4)	
Other government	1.2 (1.0–1.4)	
Not insured	Reference	0
Income		
High	1.2 (1.1–1.2)	
Middle	1.0 (1.0–1.1)	
Low	Reference	0
Facility type		
Academic/research program	1.7 (1.6–1.8)	
Comprehensive community cancer program	1.2 (1.2–1.3)	
Community cancer program	Reference	0
SSS		722

[a] The SSS was created by multiplying the logarithm (ln) of the odds ratios by 100 and adding the total. The sample SSS is provided for a 50-year-old, black man with stage IIIA (T4 N0 M0) NSCLC NOS, with Charlson-Deyo Index = 0 and belonging to the reference group for all remaining factors. His SSS is 722 and estimated probability of surgical treatment is 4.5%. The sample SSS calculation for the patient described: ((ln 14.3 × 100) + (ln 15.6 × 100) + (ln 6.1 × 100)) = 722.

CI = confidence interval; NOS = not otherwise specified; NSCLC = non-small cell lung cancer; SSS = Surgical Selection Score.

Overall, AJCC metastatic status, AJCC nodal status, and age were the strongest predictors of patient selection for an operation in the SSS. Intentionally, AJCC stage group (as a single variable) was not used in the SSS. This will allow for use of the SSS in patients whose stage group may be in question at the time of treatment decisions. Our findings are not surprising, because these factors are known to favorably influence prognosis, reinforcing the concept that patients with an expectation of greater survival are offered higher-risk treatments. In fact, the independent relationship between lower metastatic status, nodal status, and younger age with longer survival is well established in clinical trials and also in previously created prediction models [7, 15–17].

For example, in a pooled analysis of patients from North Central Cancer Treatment Group Trials, a prediction model for OS and time to progression was developed for stage IIIB and IV patients, which was developed to screen patients for benefit from phase II clinical trials [17]. High white blood cell count, anemia, decreased performance status, body mass index of less than 18.5 kg/m^2, and stage IV disease were predictive of worse OS and time to progression. Although these individual-level clinical factors are not currently available in the NCDB, this model was developed in only 1,053 patients and did not include stage IIIA patients, in contrast to the SSS.

Schild and colleagues [16] developed a second prediction model of survival for patients with NSCLC. In this model, quality of life, age, performance status, primary tumor diameter, nodal status, distant metastases, and smoking cessation were significant prognostic factors for OS [16]. These authors found longer survival in patients with higher scores on their prediction model, but the model was not used to assess for likelihood of receiving

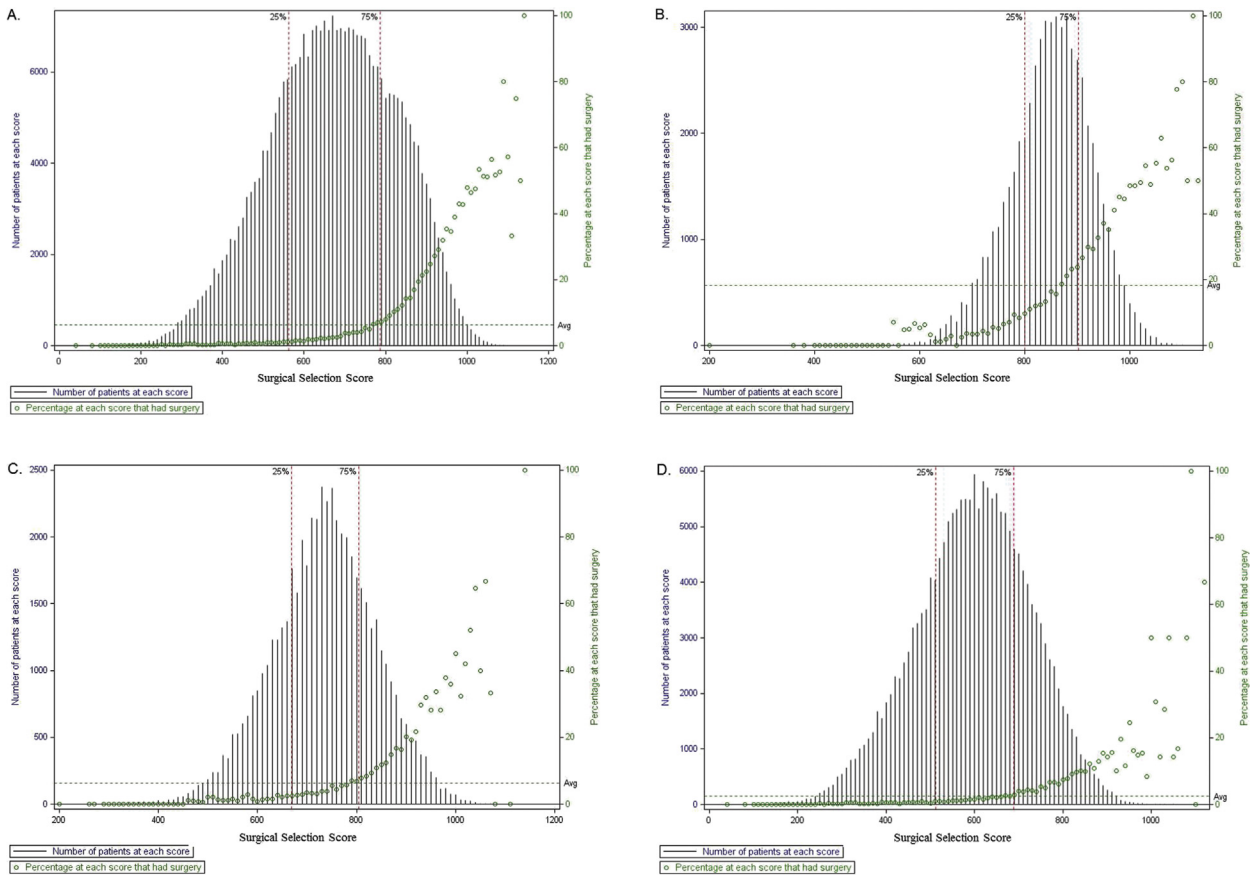

Fig 4. Distribution of Surgical Selection Score and probability of undergoing surgical intervention for the (A) entire cohort and by (B) stage IIIA, (C), stage IIIB, and (D) stage IV.

surgical resection or the effect of resection on outcomes after controlling for prognostic factors.

In our study, stratification of patients by the SSS score demonstrates not only longer survival in patients with higher SSS scores but also superior OS for surgical patients compared with nonsurgical patients after controlling for SSS. Notably, we observed two- to threefold higher median survival time for surgical patients within all quartiles of SSS. Although these results are similar to other studies that have demonstrated improved survival for advanced-stage NSCLC patients whose treatment regimens include resection, this is the first study to derive and quantitate a SSS that allows for a comparison of selection bias on survival outcomes as well as survival outcomes among patients who have similar probabilities of receiving an operation [4–6].

A key strength of this study is the use of detailed clinical information from both operative and nonoperative cohorts using a robust and statistically powerful sample. This approach avoids potential pitfalls of highly curated specialty or institutional databases that may provide granular data but are limited by institutional and referral biases that may limit the generalizability of their findings [10, 18].

We recognize that many prediction models have been developed to predict outcomes for NSCLC patients, including survival after resection, pathologic N2 disease, postoperative morbidity and recurrence, and selection of proper candidates for postoperative radiotherapy with pathologic N2 disease. However, no studies have used selection for surgical therapy as their primary outcome [19–23].

As with other studies using administrative/registry data sets, such as the NCDB, acknowledging the limitation is important. A principle limitation of our study is that the data set did not specify the intent for which the surgical intervention was performed. For this reason, we prospectively limited the surgical procedures we included in the analysis to those that would have likely been undertaken for curative intent or improved oncologic outcome, or both, rather than for palliation or diagnosis. However, it is possible that some diagnostic procedures were analyzed despite this inclusion criterion. Given that outcomes remained superior in the surgical cohort, we do not think that this potential bias was a major determinant of outcomes because the null hypothesis was nevertheless rejected.

In addition, the NCDB does not currently capture data on patient smoking status. Although smoking status is a predictor of perioperative morbidity and death and influences surgical decision making, we do not believe that this is a major factor in surgical selection, particularly if

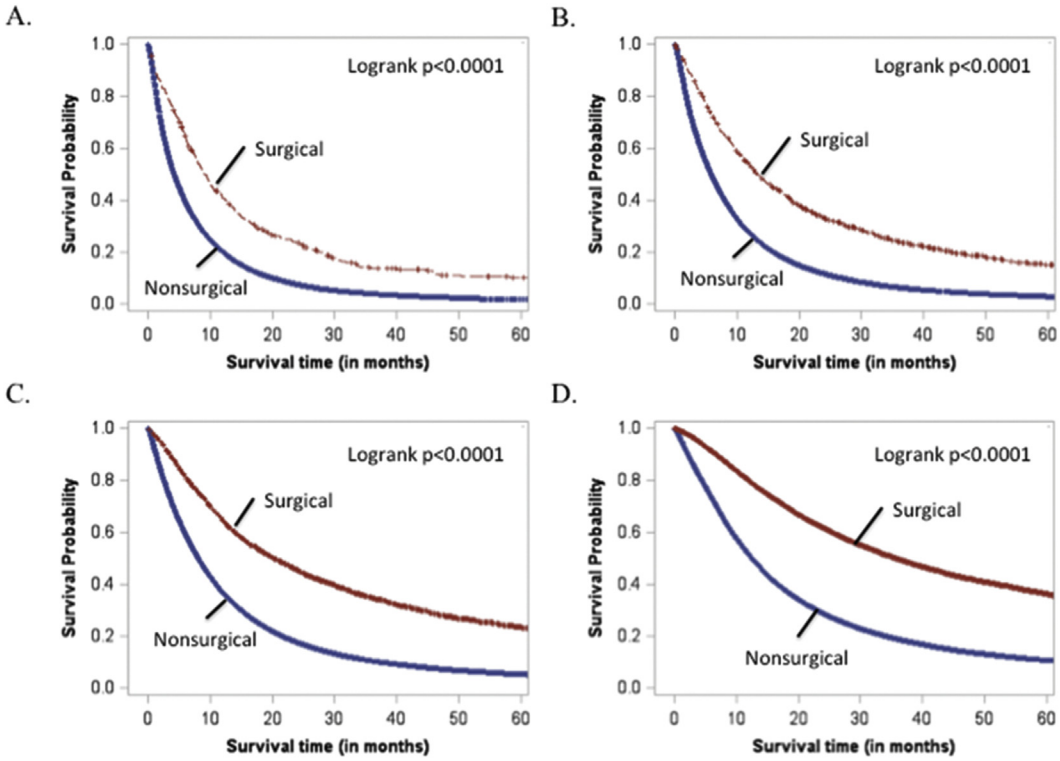

Fig 5. Kaplan-Meier survival analysis of patients stratified by treatment group by (A) the lowest, (B) second, (C) third, and (D) fourth Surgical Selection Score quartile.

smoking cessation can be achieved. This is an important question for future research [24, 25].

Although the SSS has potential application to guide therapeutic decision making by guiding referrals to surgeons, further work to delineate its stage-specific functionality and external validation is needed before it can be applied in this fashion. We acknowledge that the SSS does not indicate that a patient has resectable disease, because the data required for this assessment are not available in a large administrative data set; however, we do feel that it can be used as a guide to identify patients who should be evaluated for resection.

Selection bias includes known and unknown confounders, and the unknown confounders, such as disease burden, molecular factors, patient preferences, and nuances of comorbidities beyond the Charlson-Deyo Index, are not captured in the SSS because they are not currently captured anywhere. However, the strength of the SSS to be used as a prospective tool may provide an important decision-making adjunct for nonsurgeons who do not have immediate access to a surgeon. Ultimately, randomized clinical trials are needed to clarify the therapeutic role of resection for advanced-stage NSCLC patients, but we believe the SSS is an important stepping-stone toward the design of such trials by allowing for the prospective identification of patients who have a high likelihood of benefitting from surgical resection to assist with accrual to such trials.

In conclusion, the SSS we have created predicts with high accuracy the likelihood of undergoing resection in advanced NSCLC patients. When stratified by the SSS, we demonstrate that patients undergoing resection have superior survival within all quartiles of the SSS. Once further validated using additional data sets and prospectively tested in clinical settings, we believe this model can be used to identify advanced-stage NSCLC patients who will likely benefit from consideration for surgical intervention as part of multimodality therapy.

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Audio Discussion: Audio of the discussion that followed the presentation of this paper at the STS Annual Meeting can be accessed in the online version of this article [http://dx.doi.org/10.1016/j.athoracsur.2017.05.071] on http://www.annalsthoracicsurgery.org.

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