



Development and Validation of a Deep Learning Model for Non–Small Cell Lung Cancer Survival

Journal Club 2021 on Friday 15 January 2021

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Objectives

- To compare the performances of **DeepSurv**, a deep learning survival neural network with a tumor, node, and metastasis staging system in the prediction of survival
- Test the reliability of individual treatment recommendations provided by the deep learning survival neural network



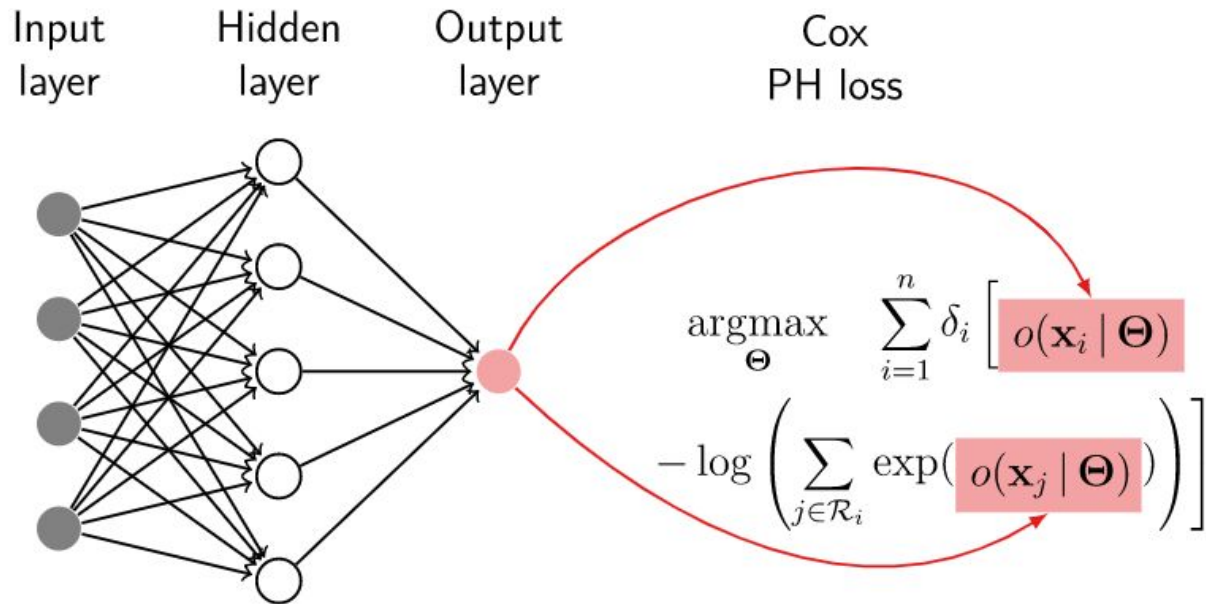
Introduction

Linear Survival Analysis (linear log-risk functions)

- Cox's Proportional Hazards Model

Non-linear Survival Analysis (nonlinear log-risk functions)

- classification methods
- time-encoded methods
- risk-predicting methods

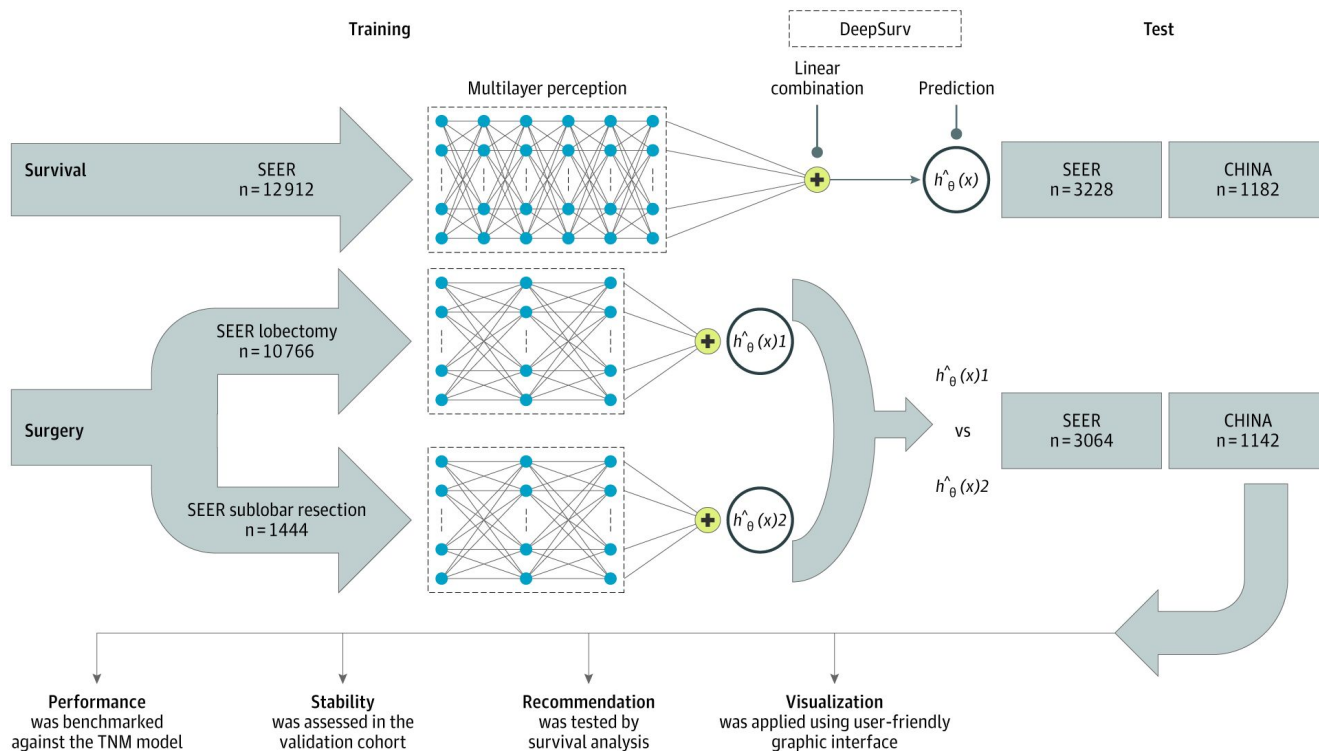


Faraggi-Simon's network: the model be extended to the non-linear case by replacing the linear predictor with the output of a neural network with parameters Θ .



Design, Setting & Participants

- Population-based cohort study
- Totally 17,322 patients, 127 features, including patient characteristics, tumor stage, and treatment strategies
- 12,912 patients (training set) + 3,228 patients (internal validated set) with stages I to IV NSCLC (January 2010 - December 2015) from Surveillance, Epidemiology, and End Results database (SEER)
- 1,182 patients (externally validated set) with stage I to III NSCLC (January 2009 - December 2013) in Shanghai Pulmonary Hospital (CHINA)



Four further experiments were conducted on the networks to test their performances against tumor, node, and metastasis (TNM) models



TNM Staging Model

T (Tumor) = refers to the size and extent of the primary tumor

N (Node Involvement) = refers to the the number of nearby lymph nodes that have cancer

M (Metastasis) = refers to whether the cancer has metastasized. This means that the cancer has spread from the primary tumor to other parts of the body

Staging	T	N	M
Stage 0	T is	N0	M0
Stage 1	T1	N0	M0
Stage II A	T0	N1	M0
	T1	N1	M0
	T2	N0	M0
Stage II B	T2	N1	M0
	T3	N0	M0
Stage III A	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage III B	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage III C	Any T	N3	M0
Stage IV	Any T	Any N	M1



Cox proportional hazards model

The hazard function $\lambda(t|x) = \lambda_0(t) \cdot e^{h(x)}$

Where:

- a baseline hazard function, $\lambda_0(t)$
- a risk score, $r(x) = e^{h(x)}$, defined as the effect of an individual's observed covariates on the baseline hazard
- $h(x)$ as the log-risk function

To estimate the log-risk function, $h(x)$, by a linear function, $\hat{h}_\beta(x) = \beta^T x$ or $\hat{r}_\beta(x) = e^{\beta^T x}$



DeepSurv

- Cox proportional hazards deep neural network
- Deep feed-forward neural network which predicts the effects of a patient's covariates on the hazard rate
- Personalized treatment recommender system

The hazard function $\lambda(t|\mathbf{x}) = \lambda_0(t) \cdot e^{h(\mathbf{x})}$

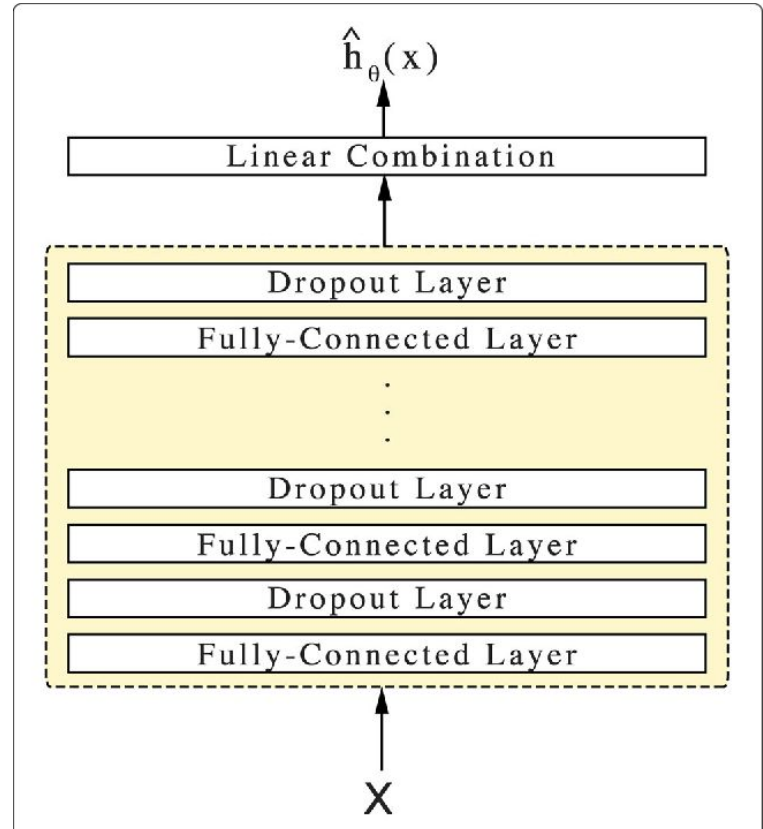
Where:

- a baseline hazard function, $\lambda_0(t)$
- a risk score, $r(\mathbf{x}) = e^{h(\mathbf{x})}$, defined as the effect of an individual's observed covariates on the baseline hazard
- $h(\mathbf{x})$ as the log-risk function

To estimate the nonlinear log-risk function, $h(\mathbf{x})$, by an **output of deep neural network**

DeepSurv

- The hidden layers consist of fully-connected nonlinear activation functions followed by dropout.
- The output of the network is taken as the predicted log-risk function $\hat{h}_\theta(x)$





Characteristics of Patients in the Data Sets

LCSS = lung cancer-specific survival

T = tumor

N = node

M = metastasis

SEER = Surveillance, Epidemiology, and End Results cancer registry

Characteristic ^a	Data set, No. (%)		
	Training	SEER (test 1)	CHINA (test 2)
Age at diagnosis, median (range), y	68 (28-95)	68 (19-92)	60 (30-87)
Sex			
Female	6657 (51.6)	1639 (50.8)	642 (54.3)
Male	6255 (48.4)	1589 (49.2)	540 (45.7)
Histologic type			
Adenocarcinoma	8794 (68.1)	2243 (69.5)	948 (80.2)
Squamous cell carcinoma	4118 (31.9)	985 (30.5)	234 (19.8)
Marital status at diagnosis			
Unmarried	5304 (41.1)	1843 (57.1)	526 (44.5)
Married	7608 (58.9)	1385 (42.9)	656 (55.5)
T			
T1a	563 (4.4)	139 (4.3)	128 (10.8)
T1b	3156 (24.4)	804 (24.9)	396 (33.5)
T1c	2342 (18.1)	641 (19.9)	346 (29.3)
T2a	3258 (25.2)	791 (24.5)	208 (17.6)
T2b	594 (4.6)	141 (4.4)	56 (4.7)
T3	1994 (15.4)	445 (13.8)	40 (3.4)
T4	1005 (7.8)	267 (8.3)	8 (0.7)
N			
N0	9712 (75.2)	2439 (75.6)	1030 (87.1)
N1	1732 (13.4)	418 (12.9)	54 (4.6)
N2	1422 (11)	356 (11)	98 (8.3)
N3	46 (0.4)	15 (0.5)	0
M			
M0	12 559 (97.3)	3132 (97)	1182 (100)
M1a	143 (1.1)	41 (1.3)	0
M1b	202 (1.6)	52 (1.6)	0
M1c	8 (0.1)	3 (0.1)	0
LCSS			
Alive	10 581 (81.9)	2666 (82.6)	956 (80.9)
Dead	2331 (18.1)	562 (17.4)	226 (19.1)
Surgery to primary site			
Pneumonectomy	613 (4.7)	132 (4.1)	40 (3.4)
Lobectomy	10 766 (83.4)	2695 (83.5)	872 (73.8)
Sublobar	1444 (11.2)	369 (11.4)	270 (22.8)
None	89 (0.7)	32 (1.0)	0

Features	Weight	Features	Weight	Features	Weight
Age at diagnosis	0.5722479	CS extension (2004+)=540	0.42365953	Stage=3	-0.0717
CS tumor size (2004+)	0.6724694	CS extension (2004+)=550	0.08433475	Stage=4	-0.07168
Regional nodes examined (1988+)	-0.4995487	CS extension (2004+)=560	0.13039102	Stage=5	-0.01987
Regional nodes positive (1988+)	0.7574372	CS extension (2004+)=570	0.06113536	Stage=6	0.041379
Sex=1	-0.062900014	CS extension (2004+)=590	0.22531554	Stage=7	0.101898
Sex=2	0.1671767	CS extension (2004+)=600	0.12043501	Stage=8	0.093093
Histologic Type ICD-O-3=0	0.055728845	CS extension (2004+)=610	-0.90538454	Stage=9	0.104782
Histologic Type ICD-O-3=1	-0.048216447	CS extension (2004+)=680	-0.824522	Stage=10	0.034815
Histologic Type ICD-O-3=2	0.015860233	CS extension (2004+)=700	0.16996412	Stage=11	0.51159
Histologic Type ICD-O-3=3	-0.08446639	CS extension (2004+)=705	-0.9847599	T8=1	0.209211
Histologic Type ICD-O-3=4	0.0417398	CS extension (2004+)=710	0.3103478	T8=2	0.038959
Histologic Type ICD-O-3=5	-0.00887268	CS extension (2004+)=730	-0.20042646	T8=3	0.056467
Histologic Type ICD-O-3=6	0.025923487	CS extension (2004+)=740	0.81883913	T8=4	0.049242
Histologic Type 2=1	-0.028282069	CS extension (2004+)=745	0.40200815	T8=5	0.06238
Histologic Type 2=2	0.020090567	CS extension (2004+)=750	0.16024342	T8=6	-0.09599
Grade=1	-0.002670259	CS extension (2004+)=770	-0.86313397	T8=7	-0.12861
Grade=2	0.063437365	CS extension (2004+)=785	-0.17053518	N8=1	-0.06939
Grade=3	0.15810749	CS mets at dx (2004+)=0	-0.07108595	N8=2	0.052847
Grade=4	-0.124901354	CS mets at dx (2004+)=15	0.14313275	N8=3	0.070122
RX Summ - Scope Reg LN Sur (2003)	-0.05786139	CS mets at dx (2004+)=16	0.08157881	N8=4	0.202186
RX Summ - Scope Reg LN Sur (2003)	0.029179208	CS mets at dx (2004+)=17	-0.34559816	M8=1	-0.21266
RX Summ - Scope Reg LN Sur (2003)	0.020770853	CS mets at dx (2004+)=18	0.059344094	M8=2	-0.02519
RX Summ - Scope Reg LN Sur (2003)	-0.03520994	CS mets at dx (2004+)=20	-0.12556794	M8=3	0.030704
CS extension (2004+)=100	-0.0725175	CS mets at dx (2004+)=21	0.99101025	M8=4	0.576268
CS extension (2004+)=110	0.04731824	CS mets at dx (2004+)=23	-0.19575515	Marital status at diagnosis=0	0.034368
CS extension (2004+)=115	0.026038347	CS mets at dx (2004+)=24	-0.037997384	Marital status at diagnosis=1	-0.10559
CS extension (2004+)=120	0.004864246	CS mets at dx (2004+)=25	-0.76219594	Lung - Pleural/Elastic Layer Invasion (PL) by H and E or Elastic Stain=0	0.001433
CS extension (2004+)=125	-0.09474413	CS mets at dx (2004+)=26	0.90065193	Lung - Pleural/Elastic Layer Invasion (PL) by H and E or Elastic Stain=1	0.034629
CS extension (2004+)=200	0.021685144	CS mets at dx (2004+)=30	-0.18796362	Lung - Pleural/Elastic Layer Invasion (PL) by H and E or Elastic Stain=2	0.001899
CS extension (2004+)=210	-0.16040157	CS mets at dx (2004+)=32	0.6542427	Lung - Pleural/Elastic Layer Invasion (PL) by H and E or Elastic Stain=3	0.164463
CS extension (2004+)=220	-0.10082796	CS mets at dx (2004+)=33	-1.1801782	Lung - Separate Tumor Nodules - Ipsilateral Lung=1	-0.03875
CS extension (2004+)=230	-0.21979994	CS mets at dx (2004+)=36	0.88033414	Lung - Separate Tumor Nodules - Ipsilateral Lung=2	0.063924
CS extension (2004+)=300	-0.033153117	CS mets at dx (2004+)=37	-0.1698591	Lung - Separate Tumor Nodules - Ipsilateral Lung=3	0.042076
CS extension (2004+)=400	-0.029358057	CS mets at dx (2004+)=40	0.14898834	Lung - Separate Tumor Nodules - Ipsilateral Lung=4	0.150139
CS extension (2004+)=410	-0.102100626	CS mets at dx (2004+)=41	0.5691616	Lung - Surgery to Primary Site (1988-2015)=1	0.005233
CS extension (2004+)=420	-0.07669448	CS mets at dx (2004+)=42	0.032155376	Lung - Surgery to Primary Site (1988-2015)=2	-0.13327
CS extension (2004+)=430	0.057814617	CS mets at dx (2004+)=43	0.030705813	Lung - Surgery to Primary Site (1988-2015)=3	-0.03041
CS extension (2004+)=440	0.22026922	CS mets at dx (2004+)=51	0.6830787	Lung - Surgery to Primary Site (1988-2015)=4	0.141988
CS extension (2004+)=455	-0.01990803	CS mets at dx (2004+)=52	1	Lung - Surgery to Other Regional/Distant Sites (1998+)=1	-0.04313
CS extension (2004+)=460	-0.061044298	CS mets at dx (2004+)=53	0.6274554	Lung - Surgery to Other Regional/Distant Sites (1998+)=2	0.117256
CS extension (2004+)=465	0.56912345	CS mets at dx (2004+)=70	-0.58639836	Lung - Surgery to Other Regional/Distant Sites (1998+)=3	0.06074
CS extension (2004+)=500	-0.10761972	Stage=1	-0.4348911		
CS extension (2004+)=520	0.20671241	Stage=2	-0.15681928		

Feature Component Weights in the DeepSurv Model



Comparison of TNM Stage and DeepSurv Model for Survival Prediction in Test Data Sets

LCCS = lung cancer-specific survival

NA = not applicable;

SEER = Surveillance, Epidemiology, and End Results cancer registry

TNM = tumor, node, and metastasis

LCCS outcome	Model	C statistic (95% CI)	P value
SEER	TNM	0.706 (0.681-0.731)	NA
	DeepSurv	0.739 (0.713-0.764)	<.001
CHINA	TNM	0.691 (0.659-0.724)	NA
	DeepSurv	0.742 (0.709-0.775)	<.001
Treatment	DeepSurv (lobectomy, SEER)	0.725 (0.698-0.751)	NA
	DeepSurv (sublobar resection, SEER)	0.698 (0.672-0.725)	NA

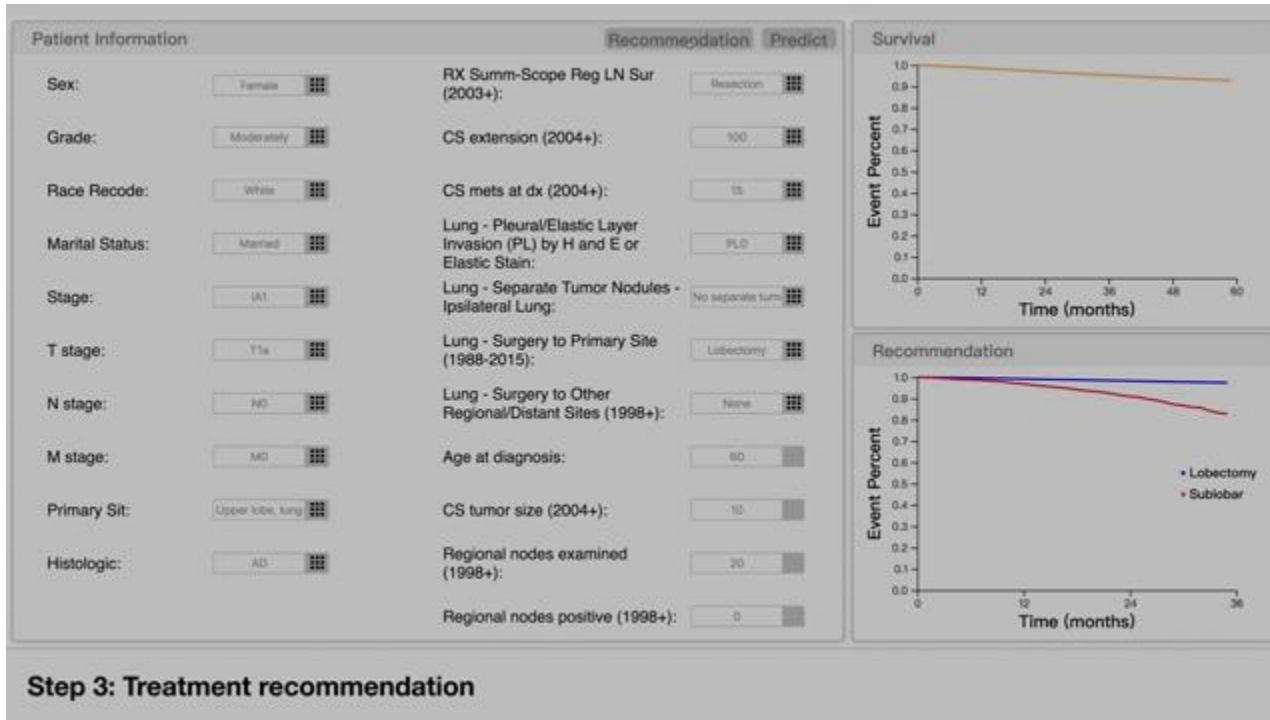


Survival Predictors in Cox PH Model

- C statistic for Cox proportional hazard regression model = 0.716 (95% CI = 0.705-0.727)
- C statistic for DeepSurv model = 0.739 (95% CI = 0.713-0.764)

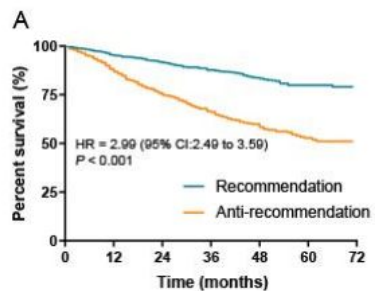
Variables	HR	95% CI	β	P value
Age at diagnosis	1.022	1.017-1.026	0.022	<0.001
Sex	1.429	1.310-1.558	0.357	<0.001
Histologic	1.151	1.053-1.258	0.141	0.002
Grade	0.911	0.869-0.955	-0.093	<0.001
RX Summ-Scope Reg LN Sur (2003+)	0.895	0.825-0.972	-0.111	0.008
CS tumor size (2004+)	1.009	1.006-1.011	0.009	<0.001
CS extension (2004+)	1.039	1.008-1.071	0.039	0.013
CS mets at dx (2004+)	0.973	0.948-0.999	-0.027	0.039
Regional nodes examined (1988+)	0.987	0.981-0.992	-0.013	<0.001
Regional nodes positive (1988+)	1.053	1.035-1.071	0.051	<0.001
Stage	1.272	1.214-1.334	0.241	0.001
T stage	0.926	0.881-0.974	-0.076	0.003
N stage	1.148	1.055-1.248	0.138	0.001
M stage	2.066	1.240-3.443	0.726	0.005
Marital status	0.791	0.727-0.861	-0.234	<0.001
Lung-Pleural/Elastic Layer Invasion (PL) by H and E or Elastic Stain	1.109	1.044-1.179	0.104	0.001

Cox PH: Cox proportional hazard regression; HR: Hazard Ratio; CI: Confidence Interval.
 $Hx=0.022 * \text{Age at diagnosis} + 0.357 * \text{Sex} + 0.141 * \text{Histologic-Grade} * 0.093 - 0.111 * \text{RX Summ-Scope Reg LN Sur (2003+)} + 0.009 * \text{CS tumor size (2004+)} + 0.039 * \text{CS extension (2004+)} - 0.027 * \text{CS mets at dx (2004+)} - 0.013 * \text{Regional nodes examined (1988+)} + 0.051 * \text{Regional nodes positive (1988+)} + 0.241 * \text{Stage} - 0.076 * \text{T stage} + 0.138 * \text{N stage} + 0.726 * \text{M stage} - 0.234 * \text{Marital status} + 0.104 * \text{Lung - Pleural/Elastic Layer Invasion (PL) by H and E or Elastic Stain}.$

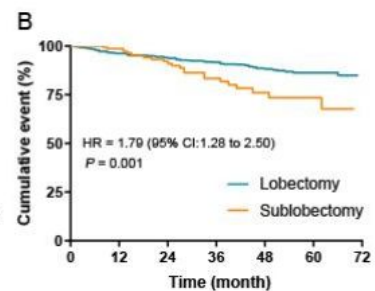


User-Friendly Interface of DeepSurv Model, Which Facilitates Survival Prediction and Treatment Recommendation

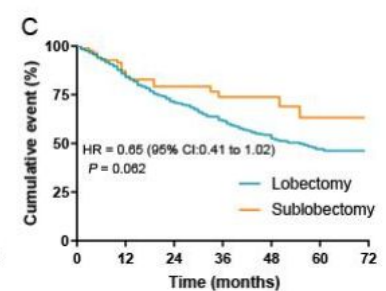
- A. Lung cancer-specific survival recommendation comparisons of SEER dataset
- B. SEER lobectomy test dataset
- C. SEER sublobar resection test dataset
- D. Lung cancer-specific survival recommendation comparisons of CHINA dataset
- E. CHINA lobectomy test dataset
- F. CHINA sublobar resection test dataset



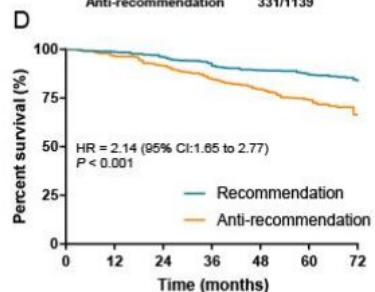
	Events/N
Recommendation	208/1925
Anti-recommendation	331/1139



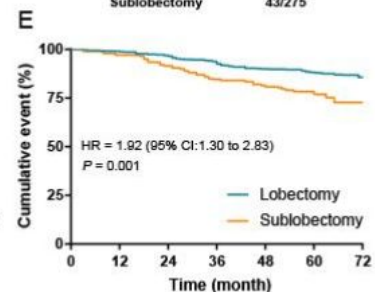
	Events/N
Lobectomy	188/1831
Sublobectomy	43/275



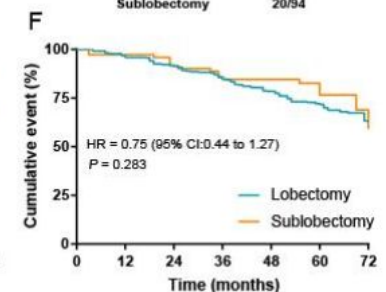
	Events/N
Lobectomy	288/864
Sublobectomy	20/94



	Events/N
Recommendation	112/751
Anti-recommendation	118/391



	Events/N
Lobectomy	70/552
Sublobectomy	42/199



	Events/N
Lobectomy	102/320
Sublobectomy	16/71



Conclusion

- The deep learning survival neural network model (DeepSurv) showed more promising results in the prediction of lung cancer-specific survival (LCSS) than the tumor, node, and metastasis stage (TNM) on the test data set (SEER) with C statistic = 0.739 vs 0.706.
- The population who received the recommended treatments had superior survival rates than those who received treatments not recommended with hazard ratio = 2.99 (95% CI = 2.49-3.59; $P < .001$)

Q & A