



Predicting Recurrence and Second Primary Lung Cancer Following Early-Stage NSCLC Resection With the Open-Access Sybil Model

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INTRODUCTION

- Following resection of early-stage non-small cell lung cancer (NSCLC), guidelines recommend surveillance for recurrence and second primary lung cancer (SPLC) with periodic chest computed tomography (CT).
- Sybil, a validated open-access deep learning model, can accurately predict future lung cancer risk from screening non-contrast chest CTs (ncCCT) without image annotation or human input.
- We tested Sybil's ability to predict recurrence or SPLC following curative-intent resection, despite not being trained on post-resection ncCCTs.

METHODS

- This retrospective registry-based cohort study included patients who underwent resection of pathologic stage 0-IIIB NSCLC at three hospitals between January 1, 2014, and August 23, 2024.
- The outcome was the time to the composite event of SPLC or locoregional or distant recurrence.
- 1-, 2-, and 3-year Sybil risk scores for the risk of lung cancer were generated from ncCCTs obtained between 90 days and five years post-resection and compared using clustered Wilcoxon rank-sum testing.
- Landmark analysis was performed in 6-month intervals, starting at 7 months after resection and including risk scores obtained up to 2 months prior to the landmark. At each landmark, the time-dependent area under the curve (AUC) for an event (SPLC or recurrence) within 1, 2, and 3 years was estimated.
- For each of Sybil's 1-, 2-, and 3-year risk scores, Bayesian joint models were constructed linking survival probabilities and score trajectory using the JMBayes2 package. For each joint model, the time-dependent AUC for an event (SPLC or recurrence) within 1, 2, and 3 years was estimated in 6-month intervals and the association factor α was calculated, representing the log hazard ratio of a one-unit increase in the current value of the log-transformed Sybil score.

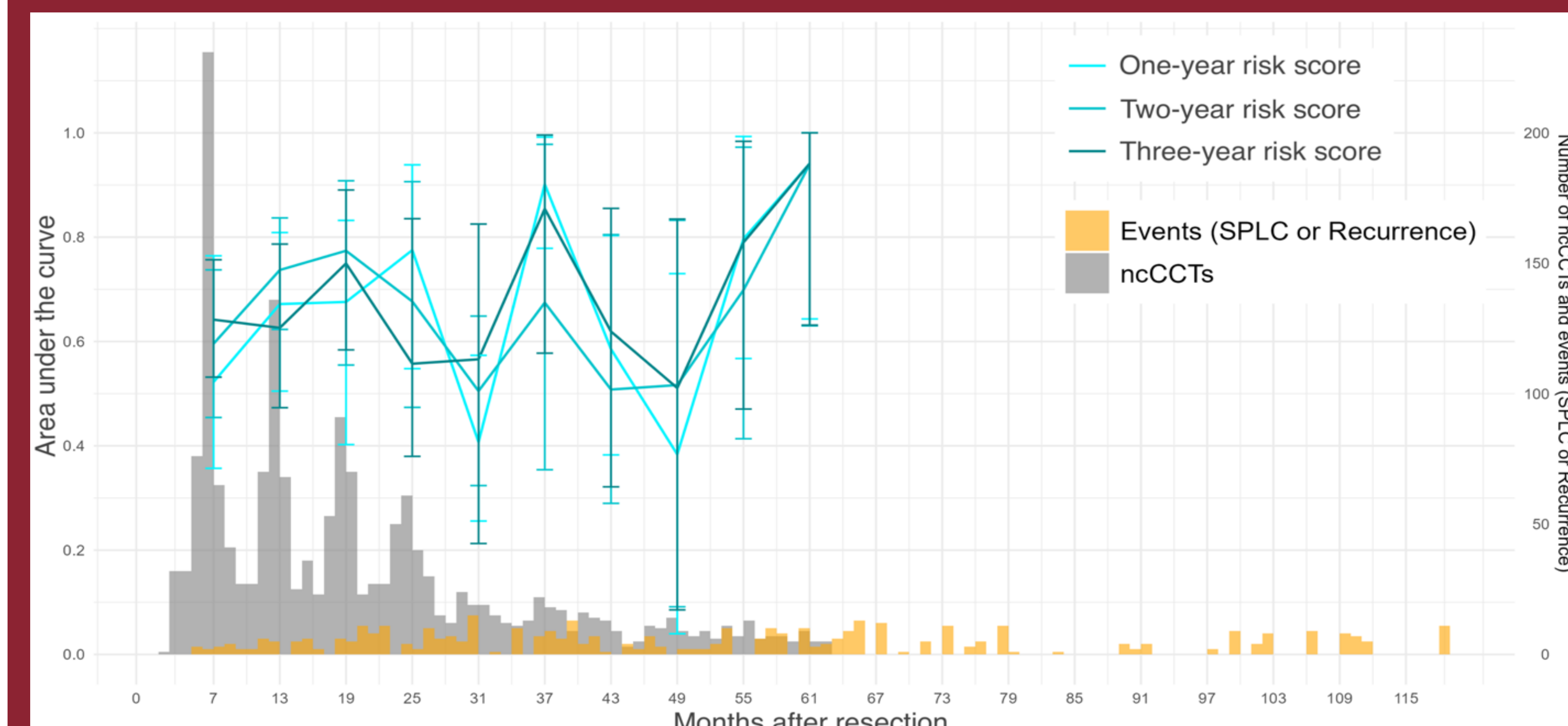
Artificial Intelligence (AI) Use Disclaimer

Initial versions of the R code used for statistical analysis were generated with the assistance of Claude Code Sonnet 5.0. All code was subsequently reviewed, edited, and validated by the authors, who verified correctness of the outputs and take full responsibility for the analysis.

RESULTS

- We included 752 patients and 1,769 ncCCTs obtained 3–63 months post resection (**Table**).
- Median one-, two-, and three-year Sybil risk scores were 0.011 (IQR, 0.004–0.022), 0.024 (IQR, 0.016–0.039), and 0.038 (IQR, 0.025–0.071), respectively.
- Patients who experienced an event (SPLC or recurrence) had higher 1-, 2-, and 3-year Sybil risk scores compared to those who did not (all $p < .001$).
- Landmark analysis showed increases in Sybil's 1-year AUC over the first 25 months post-resection and increases in Sybil's 2- and 3-year AUCs over the first 19 months post-resection, respectively (**Figure 1**).

Figure 1. Area under the curve (AUC) for 1-, 2-, and 3-year Sybil risk scores in a landmark analysis.



- Joint modeling showed a strong association between event risk (SPLC or recurrence) and one-year (α , 0.47; $p < .001$; **Figure 2**), two-year (α , 0.57; $p < .001$), and three-year (α , 0.70; $p < .001$) Sybil risk scores, respectively.

Figure 2. Area under the curve (AUC) for 1-, 2-, and 3-year Sybil risk scores using joint models linking survival probabilities and score trajectory.

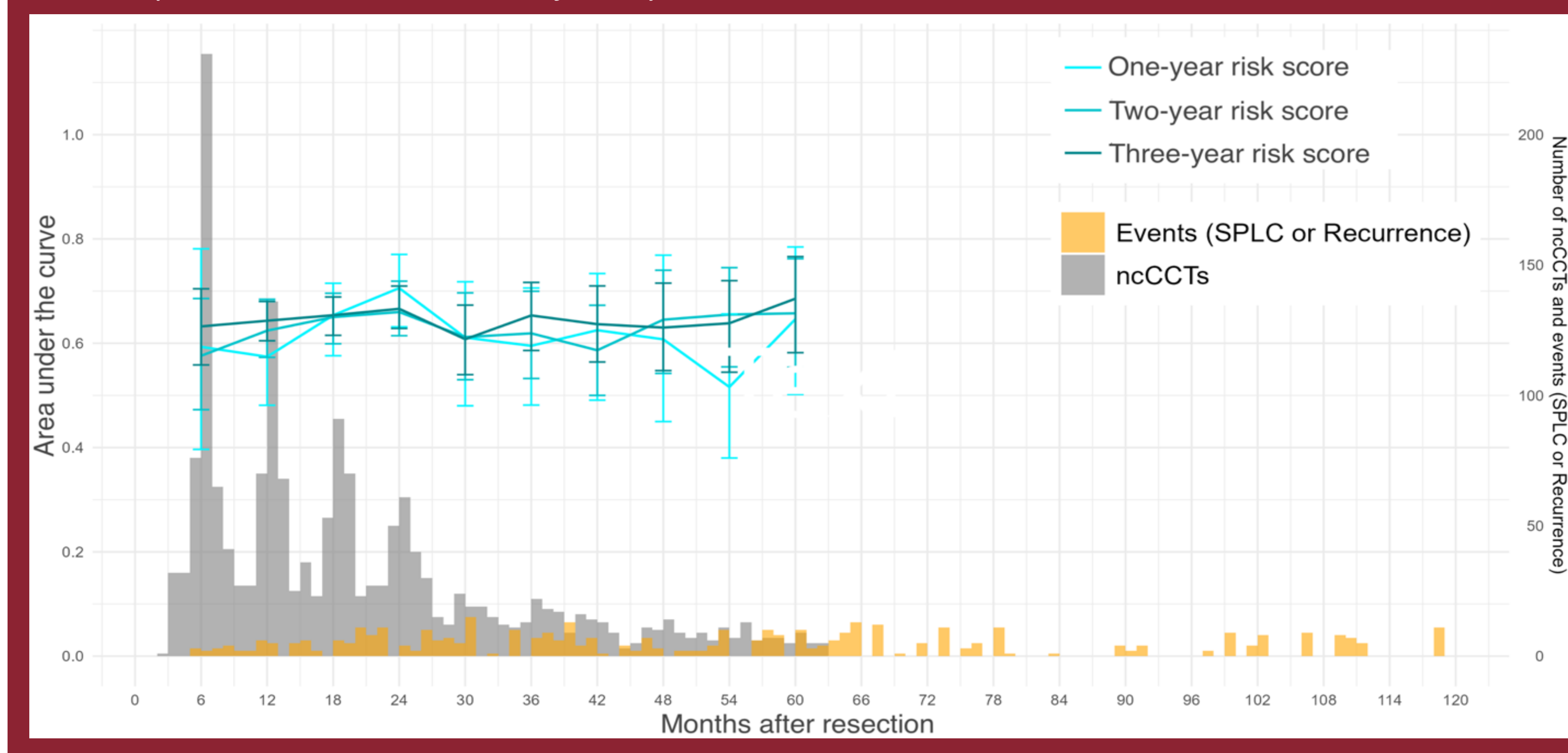


Table. Baseline characteristics of the study cohort (N=752)

Age at surgery, median (IQR)	70.0 (64.0–75.0)
Female, n (%)	476 (63)
Smoking history, n (%)	
Current	89 (12)
Former	299 (40)
Never	95 (13)
Missing	269 (36)
Pack-years, median (IQR)	40.0 (25.0–50.0)
Missing	406 (54)
Pathologic stage, n (%)	
0	20 (3)
IA	593 (79)
IB	96 (13)
IIA	9 (1)
IIB	29 (4)
Occult	2 (0.3)
TONOMO	3 (0.4)
Resection type, n (%)	
Lobectomy	426 (57)
Wedge resection	184 (24)
Segmentectomy	138 (18)
Bilobectomy	3 (0.4)
Pneumonectomy	1 (0.1)
Event, n (%)	143 (19)
Days to event, median (IQR)	1122.0 (610.5–1873.5)
Follow-up (days), median (IQR)	760.5 (553.8–1211.8)

DISCUSSION AND CONCLUSION

- Despite not being trained on post-resection ncCCTs, 1-, 2-, and 3-year Sybil scores were strongly associated with risk of SPLC or recurrence.
- Sybil may be useful for clinical risk stratification and could inform risk-adapted post-operative imaging surveillance.**