

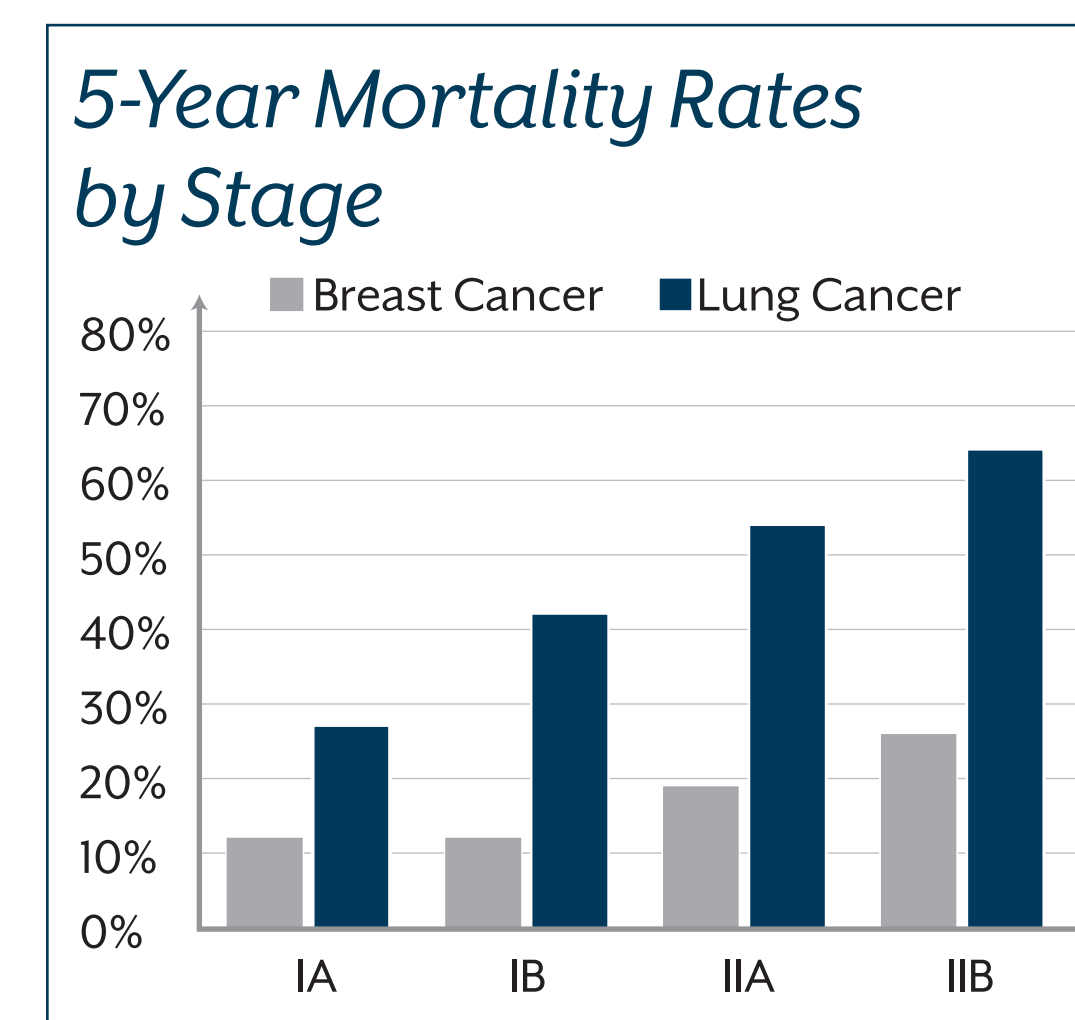
Stratification Of Resectable, Early Stage Lung Adenocarcinoma Using A Combined Molecular And Pathological Risk Estimator

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Background

- Recurrence and mortality rates in early stage, resectable lung cancer are sufficiently high to warrant consideration of post-surgical treatment.
- Given the significant, adverse side effects of adjuvant chemotherapy, novel markers to stratify patient risk are required to better assess the risk vs potential benefit of adjuvant chemotherapy.
- The aim of this study was to validate the clinical performance of a molecular measure of cancer aggressiveness in patients with early stage lung adenocarcinoma.



Methods

Cell Cycle Progression (CCP) Score:

- The CCP score is the average RNA expression of 31 CCP genes measured by qRT-PCR in FFPE samples.

Prognostic Score (PS):

- PS is the linear combination of the CCP score and pathological stage.
- $PS = 20 * (0.33 * CCP \text{ score} + 0.52 * \text{stage}) + 15$
- Stage was used as numerical variable (1=IA, 2=IB, 3=IIA, 4=IIB)
- The threshold for defining patients as high or low risk is a PS score of 27.

Patient Population:

- Primary tumors of 485 patients, surgically treated for stage I-II lung adenocarcinoma were given a CCP score and PS (patient demographics in Table 1).
- Complete surgical resection, no known neo-adjuvant treatment, no adjuvant chemotherapy or radiation within 12 weeks of surgery
- Universities of Nice, France (CHUN), Pamplona, Spain (CIMA-CUN) and Nottingham, UK (NHU)

Analysis

- Cox proportional hazards regression assessed prognostic utility with five-year lung cancer mortality as primary outcome measure.
- A PS threshold was analyzed for clinically meaningful risk discrimination by the Mantel-Cox log-rank test.

Results

Table 1. Demographic Information

	CIMA-CUN N (%)	CHU N (%)	NHU N (%)
All patients	34	318	133
Age at Diagnosis			
Median	64.0	64.8	67.0
SD	8.9	9.8	8.8
Gender			
Male	28 (82.4)	207 (65.1)	64 (48.1)
Female	6 (17.6)	111 (34.9)	69 (51.9)
Tumor size			
< 3cm	25 (73.5)	156 (49.1)	57 (42.9)
≥ 3cm	9 (26.5)	162 (50.9)	76 (57.1)
Pathological Stage			
IA	23 (67.6)	78 (24.5)	38 (28.6)
IB	7 (20.6)	145 (45.6)	43 (32.3)
IIA	2 (5.9)	61 (19.2)	38 (28.6)
IIB	2 (5.9)	34 (10.7)	14 (10.5)
Lung Cancer Death at 5 years			
Yes	4 (11.8)	40 (12.6)	31 (23.3)
No	30 (88.2)	278 (87.4)	102 (76.7)

Table 2. 5-year Lung Cancer Mortality Predicted by CCP, Stage, and PS

Events / N 75/485	Univariate		Multivariate*	
	HR (95% CI)	P value	HR (95% CI)	P value
CCP	2.41 (1.66-3.48)	2.7×10^{-6}	1.83 (1.22-2.74)	0.0029
Pathological Stage		2.5×10^{-6}		0.029
IA	1		1	
IB	4.00 (1.68-9.54)		3.28 (1.30-8.28)	
IIA	6.06 (2.45-14.94)		3.68 (1.36-10.01)	
IIB	8.49 (3.26-22.10)		3.51 (0.91-13.60)	
Prognostic Score†	2.84 (2.01-4.02)	2.4×10^{-9}	3.28 (1.62-6.63)	0.00084
Age	1.00 (0.98-1.03)	0.95	1.01 (0.98-1.03)	0.66
Gender	0.75 (0.46-1.21)	0.23	0.77 (0.46-1.30)	0.32
Tumor Size	1.23 (1.14-1.33)	1.1×10^{-5}	1.10 (0.94-1.29)	0.23
Cohort				
CHU	1		1	
CIMA-CUN	0.60 (0.22-1.69)	0.094	0.95 (0.33-2.77)	0.26
NHU	1.49 (0.93-2.39)		1.52 (0.91-2.52)	
Pleural Invasion Events/N: 74/473	1.12 (0.7-1.77)	0.64	NA	NA
Smoking Status Events/N: 74/473	0.84 (0.43-1.63)	0.61	NA	NA

* Multivariate model: $DS \sim CCP + Age + Gender + Smoking Status + TNM Stage + Adjuvant Treatment + Tumor Size + Pleural Invasion + Cohort + Stage$; Treatment

† Hazard ratio is reported per interquartile range of the PS score.

Figure 1. CCP Score by Stage

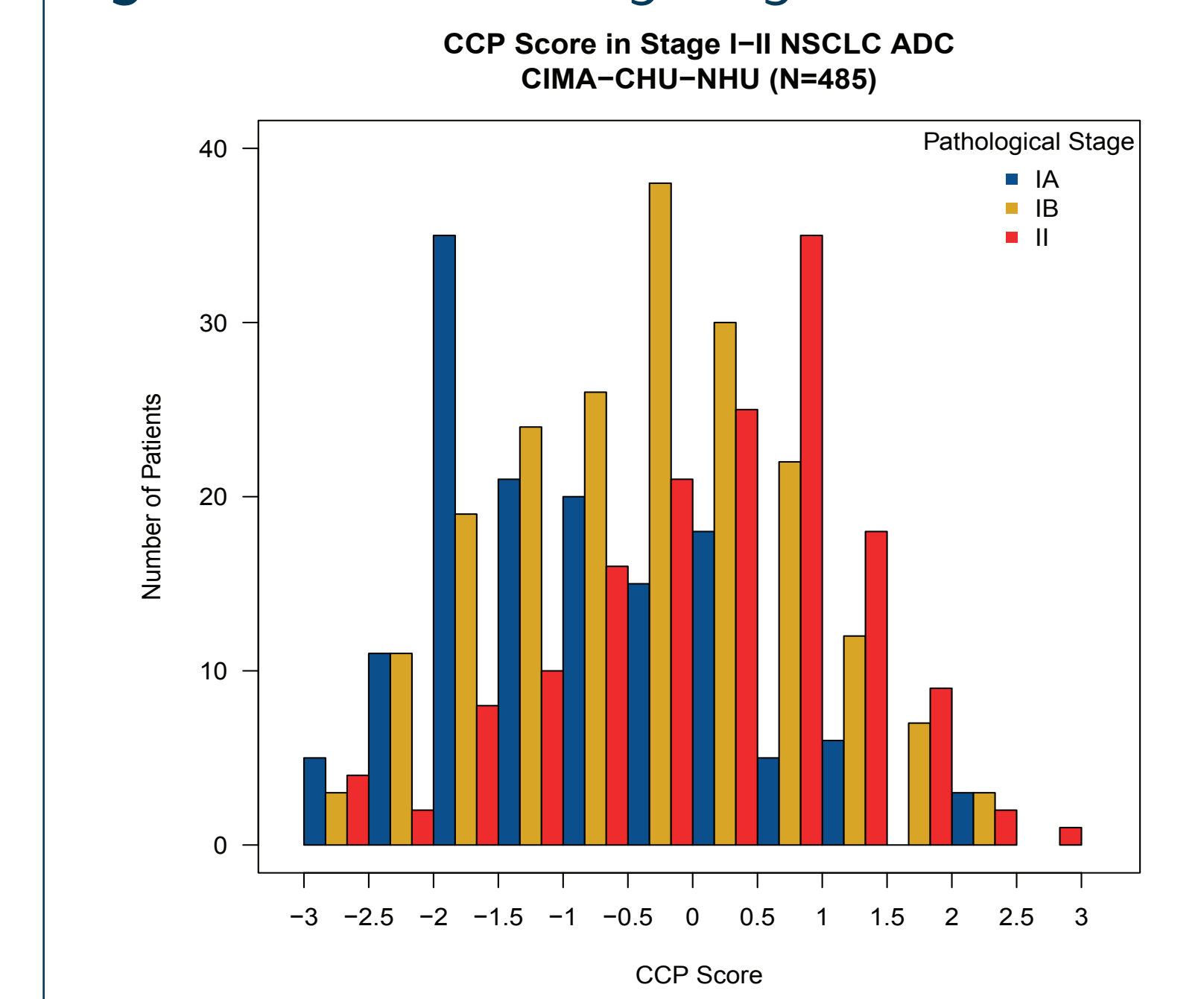
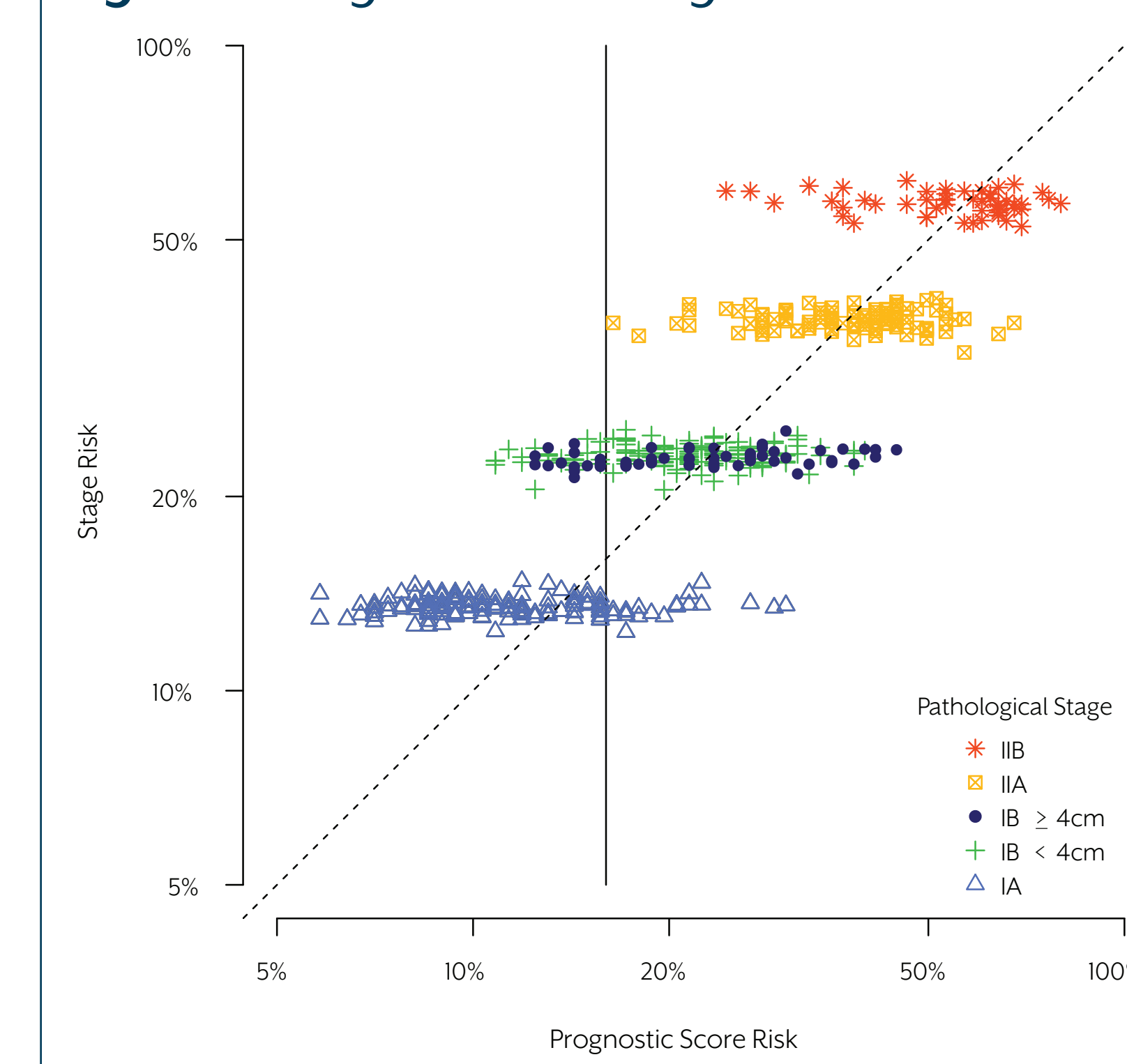


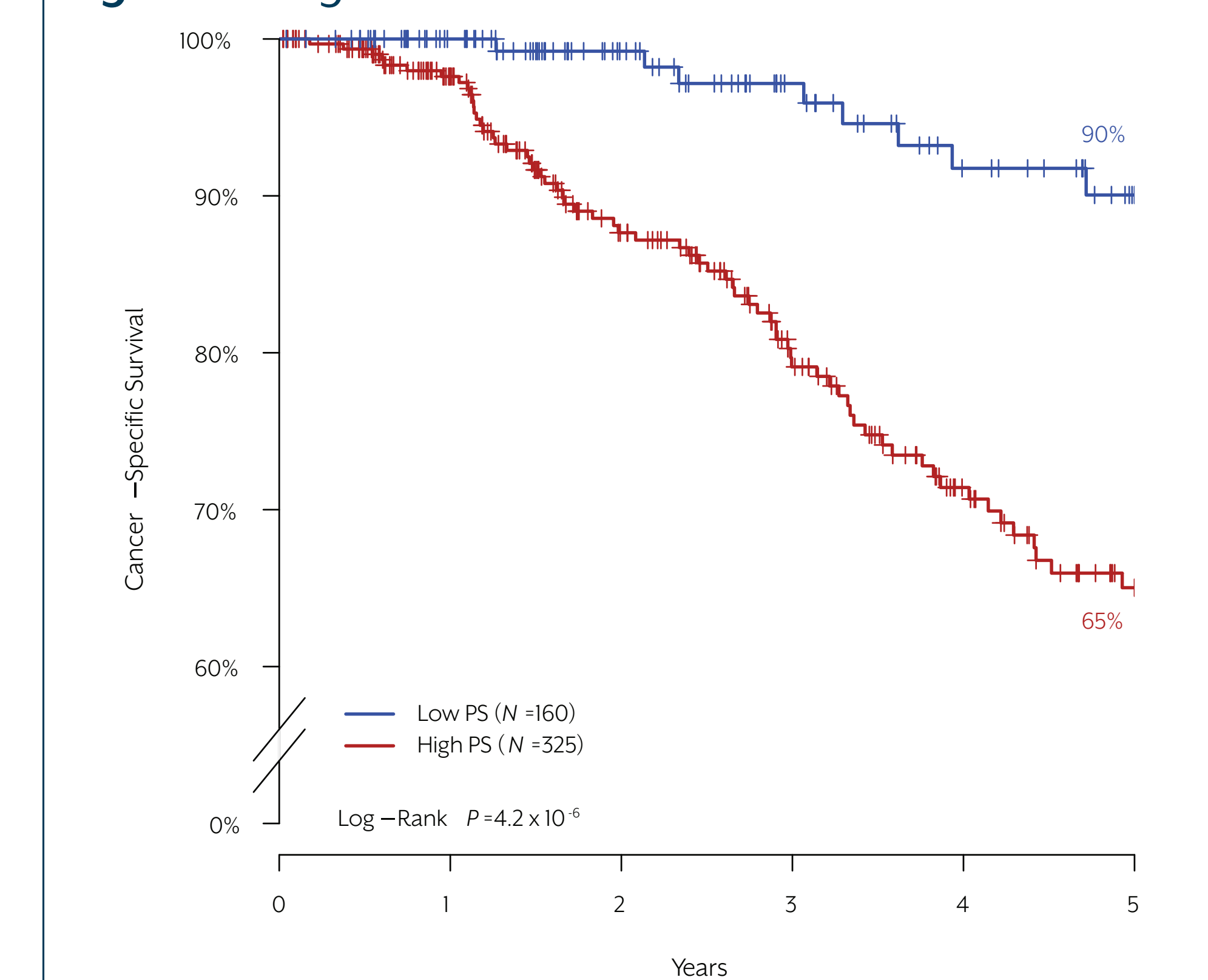
Figure 2. 5-year Mortality Risk



- The CCP score (Figure 1) added significant information above age, gender, and pathological stage in the full cohort ($p=0.0029$) (Table 2) and in stage I patients ($p=0.013$) (data not shown).
- The prognostic score improved risk discrimination compared to pathological stage alone (Table 2).
- Five-year lung cancer survival was 90% (95% CI 84%-97%) in the low risk group and 65% (95% CI 58%-73%) for the high-risk patients (log-rank $p=4.2 \times 10^{-6}$) (Table 2, Figure 3).

Results

Figure 3. High versus Low PS



Conclusions

- The CCP score is a consistent, independent prognostic marker in early stage lung adenocarcinoma.
- Patients in the low risk PS group had significantly more favorable 5-year survival than patients in the high risk PS group (Stage I & II; P -Value 4.2×10^{-6} / Stage I; P -Value 2.8×10^{-4}).
- The three-fold higher risk in the high-risk group defines a subset of patients that may be appropriate for more frequent follow-up or considered for additional treatment.

Table 3. Predicted 5-year Lung Cancer Specific Survival by PS Risk Category

Stage	Prognostic Score	Survival	Mortality
I & II	Low Risk	90%	10%
	High Risk	65%	35%
I	Low Risk	90%	10%
	High Risk	71%	29%