Prognostic score and sex-specific nomograms to predict survival in resectable lung cancer: A French nationwide study from the Epithor cohort database

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Summary

Background Prognostic assessment in patients undergoing cancer treatments is of paramount importance to plan subsequent management. In resectable lung cancer availability of an easy-to use nomogram to predict long-term outcome would be extremely useful to identify high-risk patients in the era of perioperative targeted and immune therapies.

Methods We retrieved clinical, surgical and pathological data of all consecutive patients included in Epithor, the database of French Society of Thoracic and Cardiovascular Surgery, and operated on between 2003 and 2020 for non-small cell lung cancer in a curative intent. The primary endpoint was overall survival up to 5 years. We assessed prognostic significance of available variables using Cox modelling, in the whole dataset, and in men and in women separately, and performed temporal validation. Finally, we constructed two sex-specific nomograms. Survivals by fifths of score were assessed in the development and temporal validation sets.

Findings The study included 62,633 patients (43,551 men and 19,082 women). Median survival time was 9.2 years. Nine factors had strong prognostic impact and were used to construct nomograms. The optimism-corrected c statistic for the prognostic score was 0.689 in the development sample, and 0.726 (95% CI 0.718–0.735) in the temporal validation sample. All differences between adjacent fifths of score were significant ($P < 0.0001$). Figures of 3-year OS by fifths of score were 92.2%, 83.0%, 74.3%, 64.0%, and 43.4%, respectively, in the development set and 93.3%, 88.4%, 81.0%, 73.7%, 55.7% in the temporal validation set. Performance of score was maintained when stratifying by stage of diseases.

Interpretation In the present work, we report evidence that long-term overall survival after resection of NSCLC can be predicted by an easy to construct and use composite score taking into account both host and tumour related factors.

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Keywords: Lung cancer; Surgery; Outcome; Nomogram; Survival

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Research in context

Evidence before this study

We conducted a literature search on PubMed to identify studies assessing nomograms to predict survival of patients undergoing surgery for lung cancer.

We used the search terms "nomogram", "lung cancer", "surgery", "outcomes" and "long-term survival".

We identified a study from a multi-institutional China registry of 6111 patients with resected NSCLC who received treatment between 2001 and 2008. Six independent prognostic factors (age, sex, histology, number of obtained lymph nodes, T category and N category) were identified and integrated to build a nomogram (*Liang W, Zhang L, Jiang G, et al. Development and validation of a nomogram for predicting survival in patients with resected non-small-cell lung cancer. J Clin Oncol. 2015 Mar 10;33(8):861–9*).

Another Chinese study was based on retrospective analysis of a single-institution database of 5384 patients, including both operable and not-operable non-small cell lung cancer. Age, occupation, type of health insurance, clinical TNM, central location, diagnostic method and therapeutic regimen were used to construct nomogram (*Xiao HF, Zhang BH, Liao XZ, et al. Development and validation of two prognostic nomograms for predicting survival in patients with non-small cell and small cell lung cancer. Oncotarget. 2017 Aug 2;8(38):64303–64316*).

Both studies showed the potential discriminating value of nomograms to predict survival.

Added value of this study

We analyzed data of 62,633 consecutive patients with resectable non-small cell lung cancer. Nine variables had strong prognostic impact and were used to construct prognostic nomograms.

To the best of our knowledge, we built the first sex-specific nomograms based on a nation-wide western prospective registry. Our study is the first to show that long-term overall survival after surgery for NSCLC can be predicted taking into account both host and tumour-related factors. Prognostic discrimination is strong in the whole population and in different stage subgroups.

Implications of all the available evidence

Our score and related nomograms developed for both male and female patients could represent useful, inexpensive, easy to obtain, and reproducible tools to be employed for clinical decision making. Thanks to their ability to precisely estimate patients' outcome, they could become a new standard for clinical practice.

Introduction

With a 2020 estimated incidence of 2,206,771 cases worldwide and 1,796,144 annual deaths, lung cancer remains the second more frequent cancer and first cause of cancer-related deaths.[1] Patients presenting with resectable disease continue to represent the subset of patients with non-small cell lung cancer (NSCLC) with more favorable prognosis.[2] As a general rule, patients with NSCLC are offered surgical treatment (isolated or inside a multimodality treatment approach) in case of local (stage I-II) or locally advanced but surgically resectable (stage III) disease, as well as in very selected cases of oligometastatic (stage IVa in the 8th WHO staging system) disease.[2–4] A recent analysis of the French nationwide Epithor database encompassing 54,631 consecutive patients with resectable lung cancer showed that overall 5-year survival was 58.4% and this figure was 68.9%, 53.6, and 42.3% in stage I, II, and III, respectively, underlining the need for development of effective adjuvant strategies.[5] Although pathologic stage remains the mainstay of postoperative management, its exact prognostic significance on an individual basis is a matter of debate, patients' outcome being not homogeneous within the same stage and after the same treatments.[6] This old consideration led evaluating other tumor-related factors, including histologic type or subtype, the degree of possible pleural infiltration (which is also partially taken into account in T descriptors of the TNM staging system), vascular or lymphatic emboli and aerogenous spread.[7–10] Similarly, mutations of driver oncogenes have been assessed as a prognostic indicators, with different mutations associated to more favorable or, conversely, unfavorable outcome[11]; more importantly, they represent the basis for targeted therapies, whose development in an adjuvant setting represent a major challenge in resectable lung cancer.[11–13] In recent years, the study of tumoral immune microenvironnement has gained increased interest: its composition and function has been shown to affect prognosis and it is considered as the biological basis of current immunotherapies, currently represented mainly by immune checkpoint inhibitors.[14–18] In this setting, tumor expression of PDL-1 seems to be a marker of effectiveness of anti PD1/anti PDL1 drugs, even in a perioperative setting.[16,17,19] Although tumoral immune microenvironment can be considered as the host–tumor interface, the impact of host characteristics on history of lung cancer after treatment has been less extensively studied.[20,21] Systemic inflammation on one side, patient nutritional status or fitness on the other, represent two main lines of research in this setting, increasing CRP or neutrophil/lymphocyte ratios, as well as lower BMI, albuminemia or prealbuminemia, sarcopenia or weight loss being associated with worse prognosis.[22–29] In patients with metastatic NSCLC, some host-related characteristics, including fitness and resting

energy expenditure have been shown to be associated with response to immune checkpoint inhibitors, underlining the complex interplay between host, tumor and treatments.[30,31] It seems evident that taking into account host characteristics together with tumor features should help in better assessing recurrence risk after treatments, especially surgery, and indicating perioperative treatments, in the era of immune-check point inhibitors.[18] Ideally, availability of features easy to obtain and reproducible, could represent a major advance to predict outcome, and, in particular risk of recurrence and death.[18–32] This would allow proposing perioperative treatment in a more personalized manner in order to expose to possibly toxic medications only patients likely to benefit from their administration and to avoid heavy treatments in patients less likely to develop recurrence after surgery.[18,32–36] In the present study, based on a nationwide prospectively collected database, Epithor, whose project is carried out under the auspices of the French Society of Thoracic and Cardiovascular Surgery, we developed a prognostic score and related nomogram based on nine patient and tumor-related variables. Score and nomogram appeared powerful in predicting overall survival, in the whole population of resectable lung cancer, in men and women subsets, and inside each stage-of-disease group.

Methods

The Institutional Review Board of the FSTCVS approved this Cohort study (CERC-SFCTCV-2021-02-22-Num02_ImpactIMC-Cancer). Patient consent was obtained for entry into the database, and patients were aware that these data would be used for research purposes.

To develop a prognostic score and related nomogram, we used Epithor, the French National Database of General Thoracic Surgery. Epithor was created in 2002 as a voluntary and free initiative of general thoracic surgeons in France. It is based on a prospectively filled database, endorsed by the FSTCVS. Currently, 111 centers contribute to the database, which includes the majority of surgical procedures performed in French thoracic surgical departments. The list of centers participating to Epithor shown in Supplementary Appendix. Data-quality monitoring is financially supported by the French National Cancer Institute (INCA). As a methodologically correct tool to assess surgical practices, Epithor is endorsed by the French National High Authority for Health (HAS), the governmental agency in charge of improving quality of care and guaranteeing the adequateness of the whole health care system in providing state-of-the-art care. Previous reports have focused on the technical characteristics of Epithor.[37,38] In particular, the use of hierarchic pull-down menus and the absence of free text space facilitates completeness and accuracy of the data. Routine utilities for data consistency and alerting against aberrant or contradictory values are incorporated in the software. Overall, 52 items are mandatorily collected per patient (Supplementary Appendix Table S1), covering information about the patients' characteristics, associated illness, pulmonary function, surgical procedures, cancer staging, and postoperative outcome. Some of these items correspond to specific variables (e.g., sex or age); other items correspond to availability or not of specific information and selecting availability leads to opening of specific drop-down menus (e.g., selecting availability of functional tests leads to a drop-down menu allowing entering of FEV1, FVC, FEV1/FVC ratio and DLCO). Epithor includes functions allowing participating surgeons to benchmark their activity against the national picture, by comparing the local database with the national one for completeness. This comparison is expressed through a quality score ranging from 0 to 100%. Since 2010, the accuracy of data collection is checked in regular external onsite audits. Epithor was initially developed to study perioperative outcome and collection of data on adjuvant treatments is not mandatory. Furthermore, because most French thoracic surgery facilities are inside tertiary referral hospitals, adjuvant treatments, although decided during multidisciplinary team meetings, are administered under the care of referring pneumologists or oncologists, outside of the hospitals where thoracic surgery is performed. So different protocols may be applied and they evolved over the study period. For these reasons, our study do not take into account adjuvant treatments or tumor relapse.

Patient population

Data extraction involved all consecutive patients undergoing curative lung resection for lung cancer (ICD-10-CM Coding guide C34) in participating centers. To account for the progressive implementation of the Epithor project by different surgical centers in the year 2002 and to include at least 3 years of follow-up for all the patients, we finally extracted on January, February the 15th, 2022, data of 69,790 patients aged 15 or over, who were operated on with curative intent between January 1, 2003, and December 31, 2020. After excluding patients with small-cell lung cancer (n = 346) or carcinoid tumor (n = 3310), those having only exploratory thoracotomy (n = 52) or undergoing surgery after induction (n = 2452), patients with definitive staging codified as stage 0 or occult (n = 154) and patients undergoing emergent salvage surgery (n = 43), as well as those with no follow-up beyond surgery (n = 46), the study population consisted of 63,433 patients (see Flow-chart in the Supplementary Appendix Fig. S1).

Retrieved clinical variables

Baseline demographics, comorbidities, procedure, and outcome were recorded. Patient-related variables

included age, sex, weight, height, BMI, American Society of Anesthesia score, WHO performance status, and comorbid diseases. Surgery-related variables included: side of the procedure, extent of exeresis, histologic type, and pathological staging using the International Association for the Study of Lung Cancer classification (early I–II, locally advanced III, and metastatic IV). Stage was reattributed according to the 8th TNM classification.[39]

Outcome definition

The primary endpoint was overall survival of up to 5 years. The vital status of patients was checked by the French National Institute for Statistics and Economy (INSEE) website.[40] Causes of death are not available in the INSEE website.

Statistical analysis

Descriptive data were expressed as frequency and percentage for qualitative variables, and continuous variables, as mean and standard deviation. Follow-up was counted from date of surgical intervention to the date of death from any cause or date of data cut-off (February 28, 2022), whichever occurred first. Overall survival was estimated using Kaplan–Meier product-limit method. We developed risk prediction models using Cox modelling. Models were developed in the data of patients with surgery between 2003 and 2016, and were then validated in the data from 2017 to 2020 (temporal validation). Accordingly, the follow-up was truncated as 5 years for model development, and at 3 years for validation, since almost no patient attained 5-year follow-up in the validation set. Overall, 3559 participants had at least one missing predictor value (5.7%), and missing predictor values were handled through multiple imputations by chained equations, using the baseline cumulative hazard of failure in the imputation model.[41,42] All variables considered for model development were used in the imputation model. The number of imputed datasets was fixed to the nearest integer larger than the percentage of patients with ≥1 missing predictor. Accordingly, 6 independent imputed data sets were generated and analyzed separately.[43] The convergence of the multiple imputation algorithm was assessed by visual inspection of the mean and variance of the imputation's streams. Estimates were then pooled over the 6 imputed datasets according to Rubin's rules to provide point estimates and 95% confidence intervals (CI) for each parameter.[41] Potential predictors were determined before any analysis of their association with outcome, based on expected relevance. In addition, all analyses were adjusted for 2-year periods. Fractional polynomials were used to assess whether continuous predictors could be analyzed as linear terms, and the final form was retained. Models were first derived for female and male patients separately, and interactions between sex and each predictor were tested. No other interactions were considered. The proportional hazards assumption was assessed by examination of Schoenfeld residuals and the Grambsch–Therneau test[44,45] Two strategies were used for model development with the imputed data.[46,47] First we used Wald tests for the pooled regression coefficients to simplify the model with a backward selection procedure, with P-value cut-off at 0.01, given the large sample size. Then we used a similar backward elimination procedure in each imputed dataset. The same variables (including interactions) were selected for all imputed datasets. Model performance was evaluated both by the concordance (c) statistic, as a measure of discrimination, and the calibration curve. The c statistic quantifies how well the model discriminates between patients dying and those surviving, and can be viewed as the extension of the area under the receiver operating characteristics (ROC) curve for survival data.[48] It varies between 0.5 and 1.0, where 1.0 indicates perfect discrimination. The calibration curve contrasts observed versus predicted probabilities of event to evaluate the accuracy of model predictions. The slope of the calibration curve is a measure of over-optimism of model predictions.

Since prognostic models derived from multivariable regression with variable selection are prone to overestimate regression coefficients, internal validation of our model was carried out using bootstrap.[48] The second strategy for model selection was repeated in 200 bootstrap samples and the model estimated in each bootstrap sample was then evaluated in the original sample. The differences between the performance on the bootstrap sample and the original sample were taken as a measure of the over-optimism of the selected model. The c index corrected for over-optimism was then estimated, and the calibration slope was used as a shrinkage factor for the regression coefficients of the selected model. In each case, the predictions and the estimation of model performance were estimated within the imputed datasets and then pooled (impute-last method), as recommended.[49]

Temporal validation of the model consisted in evaluating discrimination (c statistic) and calibration in the temporal validation set (2017–2020). Given the better survival observed in more recent years, a recalibration of the baseline hazard was also undertaken. The performance of the prognostic model in predicting risk was compared to that of using post-operative stage only by computing the category-less (or continuous) net reclassification index (NRIc) and the integrated discrimination improvement index (IDI).[50] Both metrics provide a measure on improvement in risk prediction, a positive value indicating better risk prediction. Confidence intervals were obtained by a resampling-perturbation procedure.[51] All tests were two-sided. Analyses were performed using the R statistical software version 4.0.5.[52]

Role of the funding source
The Epithor project is financially supported by the French Society of Thoracic and Cardiovascular Surgery.

Results
The study included 63,433 patients treated by up-front lung resection for non-small cell lung cancer between 2003 and 2020. Patients' characteristics of the whole sample, development and temporal validation groups are shown in Table 1. In the whole sample, mean age was 65.0 (9.6) years; women accounted for 30.5% of participants. Performance Status (PS) were 0, 1, 2 and 3–4 in 48.7%, 42.4%, 8.1% and 0.8% of patients, respectively. Mean BMI was 25.3 (SD 4.6), and 9021 patients (14.4%) were obese. Global Initiative for Chronic Obstructive Lung Disease (GOLD) classes were 0, 1, 2 and 3–4 in 93.5%, 2.6%, 3.5%, and 0.4% of patients, respectively, whereas American Society of Anesthesiology (ASA) categories were I, II, III and IV in 15.1%, 52.4%, 31.6% and 0.8% of cases, respectively.

The main comorbidities are listed in Table S2 and detailed for development and temporal validation sets. In the whole sample, 92% of patients have at least one significant comorbidity. Most frequent associated illness were represented by concomitant malignancy, lower limb atheroma, diabetes mellitus, ischemic heart disease, chronic heart failure, cerebrovascular disease, chronic renal insufficiency, and liver cirrhosis (in 27.9%, 10.5%, 10.3%, 8.5%, 4.6%, 3.6%, 1.9%, and 1% of cases, respectively).

Surgery was right-sided in 57.9% of patients and 8.5% of patients had pneumonectomy. Adenocarcinoma, squamous-cell, and large cell carcinoma represented the more frequent histologic types, accounting for 66.2%, 27.3%, and 4.8% of cases, respectively. Stage I, II, III, IV (oligometastatic) disease accounted for 54.3%, 19.0%, 22.1%, and 4.5% of cases, respectively.

Outcome
At cut-off date (February 28, 2022), in the whole sample, there were 24,997 deaths over a median follow-up time of 6.4 years (range, 0.3–18.4). The median survival time was 9.2 years (95% CI, 9.0–9.4 years). In the development and temporal validation sample median follow-up times were 9.7 and 2.3 years, and number of deaths were 15,261 (at 5 years) and 3466 (at 3 years), respectively.

Associations between predictors and survival are shown in Table 2 in female and male patients, respectively, as well as in the whole population. With respect to patient-related characteristics, adjusted HRs were 1.96 (95% CI 1.71–2.24) for male sex, 1.08 (1.02–1.15) per 10 years of age above 60, 8.57 (6.61–11.1) for $1/BMI^2$, 1.22 (1.15–1.31) for the presence of associated illness, 1.20 (1.17–1.23) per units of WHO performance status. Adjusted HRs were 1.15 (1.09–1.21), 1.43 (1.35–1.53), and 1.78 (1.52–2.10) for ASA scores 2, 3 and 4–6, respectively (versus ASA score 1). With respect to disease-related characteristics HRs were 1.20 (1.15–1.26) for need of pneumonectomy (versus other type of resection), and 1.26 (1.13–1.39), 0.97 (0.81–1.15), 1.52 (1.08–2.14) for squamous, large cell and sarcomatous histology (versus adenocarcinoma), respectively. Finally, adjusted HRs were 1.46 (1.28–1.67), 2.61 (1.63–4.17), 2.25 (1.97–2.58), 3.19 (2.82–3.60), 4.29 (3.65–5.05), and 4.63 (4.00–5.35) for stage IB, IIA, IIB, IIIA, IIIB-C, and IV, respectively.

A model nomogram was constructed accordingly and is shown in Fig. 1. Attributable scores range 0–165. For a given value of total score points, the figure in the top panel of Fig. 1 provides a prediction of survival at 1, 3 and 5 years.

The c statistic for the prognostic score was 0.689 in the development sample (after correction for optimism, 0.690 without correction), and 0.726 (95% CI 0.718–0.735) in the temporal validation sample. The model discriminated well both in males and females, with a slightly better performance in females (c statistic 0.729, 95% CI 0.712–0.747 for females, compared to 0.705, 95% CI 0.695–0.715 for males).

For comparison, we computed the c statistic for post-operative stage only in the temporal validation set, which was 0.674 (0.664–0.683). Compared to stage, the prognostic score therefore resulted in improved risk discrimination, with a NRIc of 0.384 (0.316–0.442) and an IDI of 0.044 (0.035–0.052).

Survivals by fifths of score were assessed in the development and temporal validation sets. Both samples were divided into five equal-sized groups. All differences between adjacent fifths were significant ($P < 0.0001$). Figures of 3-year OS were 92.2%, 83.0%, 74.3%, 64.0%, and 43.4% in the different groups, respectively in the development set and of 93.3%, 88.4%, 81.0%, 73.7%, 55.7% in the temporal validation set (Fig. 2).

Calibration curves of the model in the development and validation sets are shown in Fig. 3. Ten equal-sized groups were used to construct each of these curves. Fig. 3b shows predictions after recalibration of the baseline hazard to account for improved survival in recent years.

Stratification by stage
Performance of score was confirmed when stratifying by stage of diseases. Regression coefficients and c index of the model in the temporal validation set in each post-operative stage are shown in Table 3. Survivals by fifths of score according to post-operative stage in the temporal validation set are shown in Fig. 4, Panels a–d. For comparison, survival curves by stage of disease in the whole population are shown in Fig. 4, Panel e. As for the whole data set, the score was divided into five equal-sized groups in each stage group. For example, in stage 1, 3-year overall

	N missing (%)	Whole sample N = 62,633 NSCLC (%)	Development N = 40,848 NSCLC (%)	Temporal validation N = 21,785 NSCLC (%)
Period	0 (0)			
2003–2008		11,994 (19.1)	11,994 (29.4)	–
2009–2012		13,515 (21.6)	13,515 (33.1)	–
2013–2016		15,339 (24.5)	15,339 (37.6)	–
2017–2020		21,785 (34.8)	–	21,785 (100.0)
Sex	0 (0)			
Female		19,082 (30.5)	11,170 (27.3)	7912 (36.3)
Male		43,551 (69.5)	29,678 (72.7)	13,873 (63.7)
Age (years)	88 (0.1)	65.0 (9.6)	64.3 (9.7)	66.4 (9.1)
Height (cm)	20 (<0.1)	169.5 (8.4)	169.7 (8.3)	169.1 (8.7)
Body-mass index (kg/m^2)	42 (0.1)	25.3 (4.6)	25.2 (4.5)	25.5 (4.7)
≥30.0 kg/m^2		9021 (14.4)	5590 (13.7)	3431 (15.8)
WHO performance status	2626 (4.2)			
0		29,211 (48.7)	16,591 (43.1)	12,620 (58.7)
1		25,449 (42.4)	17,952 (46.6)	7497 (34.9)
2		4859 (8.1)	3575 (9.3)	1284 (6.0)
3–4		488 (0.8)	381 (1.0)	107 (0.5)
GOLD score	0 (0)			
0		58,546 (93.5)	39,867 (97.6)	18,679 (85.7)
1		1634 (2.6)	374 (0.9)	1260 (5.8)
2		2216 (3.5)	540 (1.3)	1676 (7.7)
3–4		237 (0.4)	67 (0.2)	170 (0.8)
ASA class	404 (0.6)			
1		9405 (15.1)	6220 (15.3)	3185 (14.7)
2		32,614 (52.4)	22,237 (54.9)	10,377 (47.8)
3		19,682 (31.6)	11,791 (29.1)	7891 (36.4)
4		528 (0.8)	293 (0.7)	235 (1.1)
Surgical procedure	0 (0)			
Pneumonectomy		5328 (8.5)	4366 (10.7)	962 (4.4)
Other		57,305 (91.5)	36,482 (89.3)	20,823 (95.6)
Stage	270 (0.4)			
IA		20,798 (33.3)	11,571 (28.4)	9227 (42.6)
IB		13,127 (21.0)	9663 (23.8)	3464 (16.0)
IIA		1176 (1.9)	235 (0.6)	941 (4.3)
IIB		10,663 (17.1)	7306 (18.0)	3357 (15.5)
IIIA		10,685 (17.1)	7437 (18.3)	3248 (15.0)
IIIB-3C		3114 (5.0)	2225 (5.5)	889 (4.1)
IV		2800 (4.5)	2243 (5.5)	557 (2.6)
Histology	232 (0.4)			
Adenocarcinoma		41,323 (66.2)	25,285 (62.1)	16,038 (73.9)
Squamous-cell carcinoma		17,028 (27.3)	12,295 (30.2)	4733 (21.8)
Large-cell carcinoma		3001 (4.8)	2327 (5.7)	674 (3.1)
Sarcomatoid carcinoma		489 (0.8)	329 (0.8)	160 (0.7)
Other		560 (0.9)	452 (1.1)	108 (0.5)
Side	268 (0.4)			
Right		36,081 (57.9)	23,353 (57.4)	12,728 (58.6)
Left		26,284 (42.1)	17,301 (42.6)	8983 (41.4)

Data are mean (SD) or n (%).

Table 1: **Characteristics of patients at time of surgery.**

	Full model				Final model	
	Female		Male		aHR (95% CI)	P
	aHR (95% CI)	P	aHR (95% CI)	P		
Male	–	–	–	–	1.96 (1.71–2.24)	<0.001
Age (per 10 yr above 60)	1.08 (1.02–1.15)	0.012	1.34 (1.31–1.37)	<0.001	1.08 (1.02–1.15)	0.005
1/(BMI^2)[a]	5.77 (3.41–9.77)	<0.001	9.81 (7.22–13.3)	<0.001	8.57 (6.61–11.1)	<0.001
Height (per 10 cm)	0.97 (0.91–1.04)	0.40	0.99 (0.96–1.02)	0.45	–	–
Comorbidities	1.25 (1.09–1.43)	0.001	1.22 (1.13–1.31)	<0.001	1.22 (1.15–1.31)	<0.001
WHO-PS (per unit)	1.13 (1.06–1.21)	<0.001	1.22 (1.18–1.25)	<0.001	1.20 (1.17–1.23)	<0.001
GOLD score 1	1.48 (1.05–2.09)	0.025	0.90 (0.74–1.11)	0.33	–	–
GOLD score 2	1.40 (1.03–1.89)	0.031	1.11 (0.95–1.29)	0.17	–	–
GOLD score 3–4	2.31 (0.86–6.18)	0.096	1.30 (0.89–1.90)	0.17	–	–
ASA score 2	1.16 (1.03–1.31)	0.016	1.14 (1.07–1.22)	<0.001	1.15 (1.09–1.21)	<0.001
ASA score 3	1.55 (1.33–1.79)	<0.001	1.41 (1.32–1.51)	<0.001	1.43 (1.35–1.53)	<0.001
ASA score 4–6	2.29 (1.52–3.44)	<0.001	1.71 (1.43–2.05)	<0.001	1.78 (1.52–2.10)	<0.001
Pneumonectomy	1.34 (1.18–1.52)	<0.001	1.19 (1.13–1.25)	<0.001	1.20 (1.15–1.26)	<0.001
Adenocarcinoma	1	–	1	–	1	–
Squamous-cell carcinoma	1.24 (1.11–1.38)	<0.001	0.99 (0.95–1.03)	0.61	1.26 (1.13–1.39)	<0.001
Large-cell carcinoma	0.98 (0.82–1.17)	0.81	1.18 (1.10–1.27)	<0.001	0.97 (0.81–1.15)	0.72
Sarcomatoid carcinoma	1.54 (1.09–2.18)	0.015	1.62 (1.37–1.91)	<0.001	1.52 (1.08–2.14)	0.017
Other histology	1.28 (0.92–1.79)	0.14	1.37 (1.17–1.61)	<0.001	1.27 (0.91–1.76)	0.15
Left side	0.96 (0.88–1.03)	0.26	1.01 (0.97–1.04)	0.78	–	–
Post-operative stage IA	1	–	1	–	1	–
Post-operative stage IB	1.47 (1.28–1.69)	<0.001	1.26 (1.19–1.34)	<0.001	1.46 (1.28–1.67)	<0.001
Post-operative stage IIA	2.63 (1.63–4.23)	<0.001	1.34 (1.04–1.72)	0.022	2.61 (1.63–4.17)	<0.001
Post-operative stage IIB	2.25 (1.96–2.58)	<0.001	1.77 (1.67–1.87)	<0.001	2.25 (1.97–2.58)	<0.001
Post-operative stage IIIA	3.18 (2.80–3.61)	<0.001	2.38 (2.25–2.52)	<0.001	3.19 (2.82–3.60)	<0.001
Post-operative stage IIIB-C	4.31 (3.64–5.10)	<0.001	3.30 (3.06–3.55)	<0.001	4.29 (3.65–5.05)	<0.001
Post-operative stage IV	4.76 (4.10–5.52)	<0.001	3.39 (3.14–3.65)	<0.001	4.63 (4.00–5.35)	<0.001
Male × age (per 10 yr above 60)	–	–	–	–	1.23 (1.16–1.31)	<0.001
Male × squamous-cell carcinoma	–	–	–	–	0.79 (0.71–0.88)	<0.001
Male × large-cell carcinoma	–	–	–	–	1.22 (1.01–1.48)	0.038
Male × sarcomatoid carcinoma	–	–	–	–	1.06 (0.72–1.55)	0.78
Male × other histology	–	–	–	–	1.07 (0.75–1.55)	0.70
Male × stage IB	–	–	–	–	0.86 (0.74–1.00)	0.044
Male × stage IIA	–	–	–	–	0.51 (0.30–0.87)	0.014
Male × stage IIB	–	–	–	–	0.78 (0.67–0.90)	<0.001
Male × stage IIIA	–	–	–	–	0.74 (0.65–0.84)	<0.001
Male × stage IIIB-C	–	–	–	–	0.76 (0.63–0.90)	0.002
Male × stage IV	–	–	–	–	0.72 (0.62–0.85)	<0.001

All results are adjusted hazard ratios in multivariable models, pooled over imputed datasets, and adjusted for the 2-year period of surgery (i.e., 2003–2004, 2005–2006, etc.), including interactions with sex. The hazard ratios for the final model are shrunk by the calibration slope (0.990). aHR: adjusted hazard ratio. [a]BMI had a non-linear effect in the models, and was modeled with a linear effect for 1/(BMI^2), BMI units being kg/m^2.

Table 2: **Association between predictors and survival.**

survival was 93.4%, 89.1%, 82.1%, 73.6%, and 64.8% according to fifths of score, respectively.

Discussion

In the present work, we report evidence that long-term overall survival after resection of NSCLC can be efficiently predicted by a composite score taking into account a limited number of easily collected parameters, concerning both host and tumor. A nomogram can be easily constructed; it could represent a practical, reproducible, and inexpensive tool to add to the large armamentarium available for management of patients with resectable NSCLC. Of note, the score performs satisfactorily not only in the whole population of resectable disease, but also in each stage subgroups. The arbitrary division of the samples into five equal-sized groups allowed us to illustrate how the prognostic score discriminated survival, and to provide a way to compare this between the development set and temporal

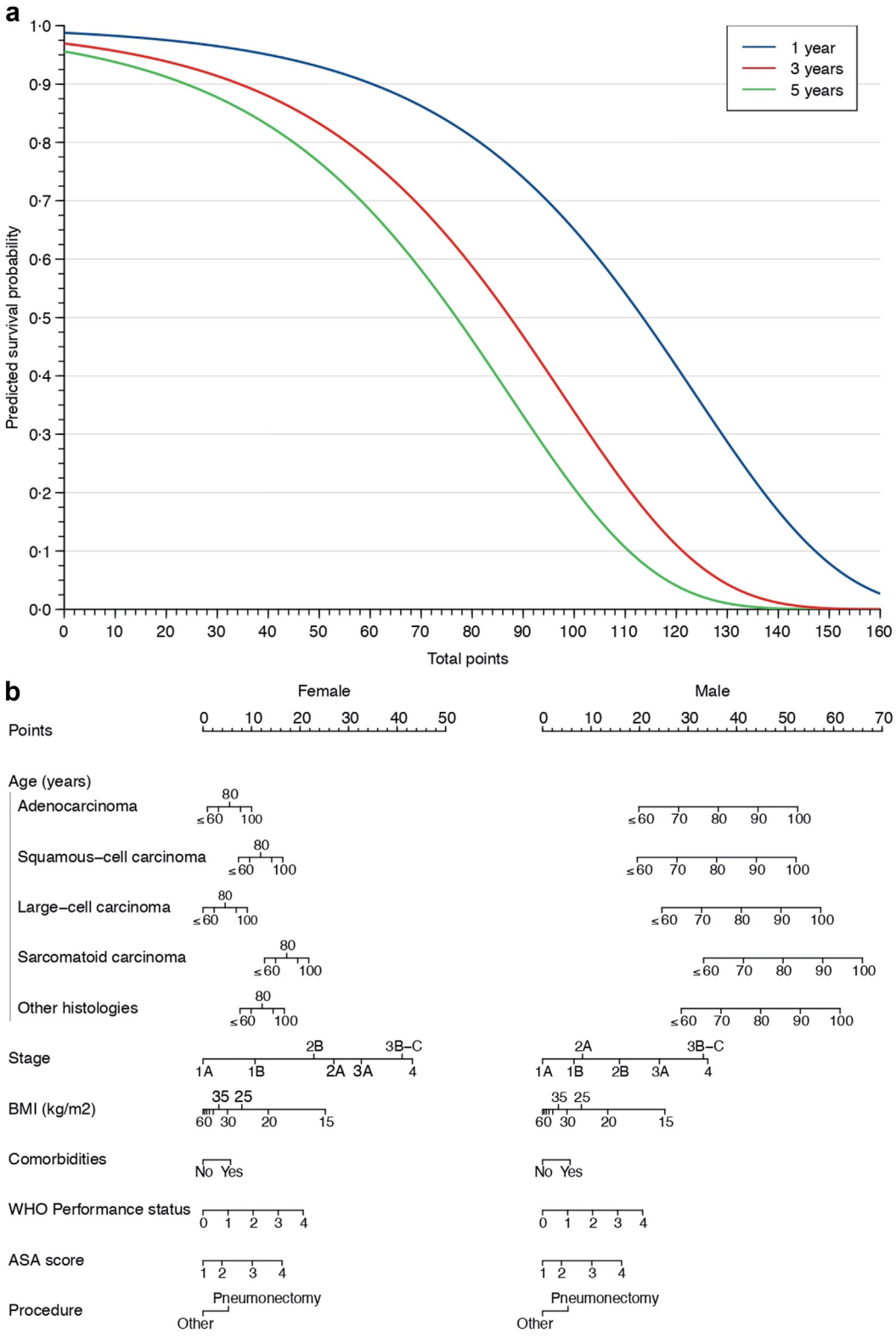

Fig. 1: **Model nomogram and prediction of survival.** For a given value of total points, the figure in the panel a provides a prediction of survival at 1, 3 and 5 years. Score points (panel b) are associated to each variable, and should be summed up. Attributable scores range 0–165. For example, a female patient aged 80 with adenocarcinoma (5 points), stage 2B (23 points), BMI 25 kg/m^2 (8 points), comorbidities (6 points),

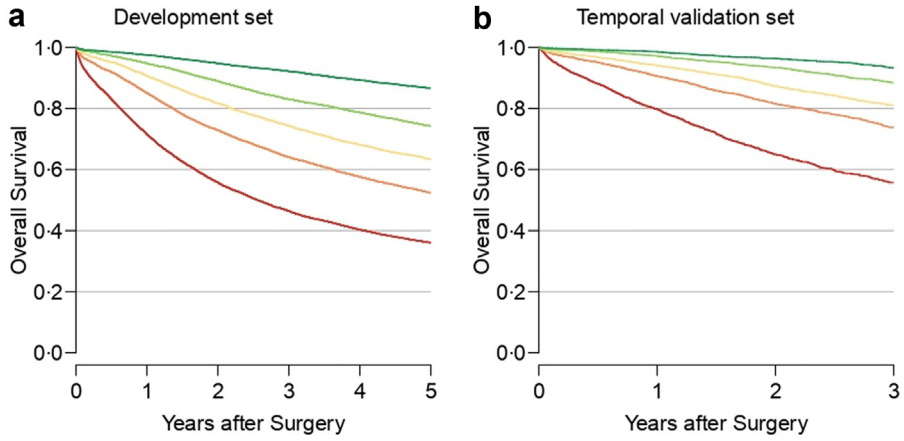

***Fig. 2:* Survival by fifths of score.** Panel a: development set; panel b: temporal validation set. Both samples were divided into five equal-sized groups. All differences between adjacent fifths are significant with P < 0.0001.

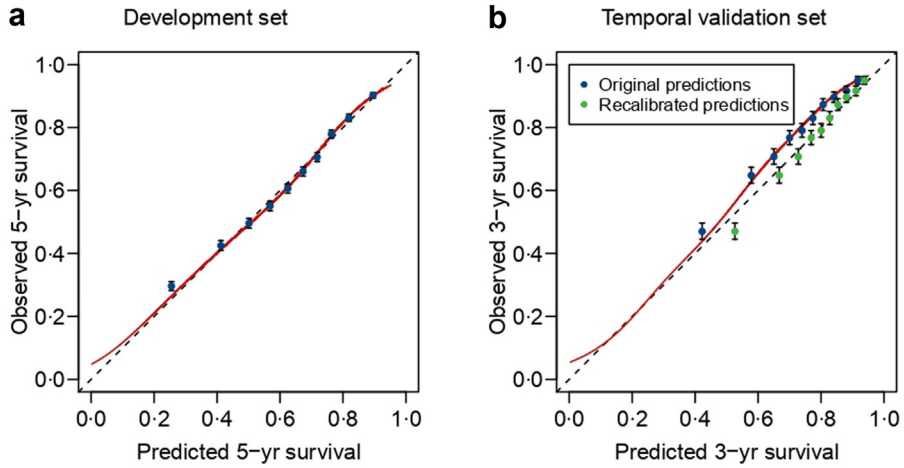

***Fig. 3:* Calibration curves of the model.** Panel a: development set; panel b: temporal validation set The blue points present observed versus average predicted survival in ten equal-sized groups, with 95% confidence intervals, and the red lines smoothed calibration curves. On panel b, the green points display the predictions after recalibration of the baseline hazard to account for improved survival in recent years.

validation set. The same categories were also used to confirm discrimination power beyond stage. Predicted survival probability for a given score can be obtained by the graph displayed together with the nomograms (Fig. 1), taking in mind that attributable scores range 0–165 and predicted survival probabilities range (approximately) 0–100% at different time points.

Two previous studies developed nomograms for prognostic assessment of patients with resectable lung cancer: a multi-institutional China registry of 6111 patients operated on between 2001 and 2008 using six prognostic factors (age, sex, histology, number of obtained lymph nodes, T category and N category),[32] and another Chinese study was based on retrospective analysis of a single-institution database of 5384 patients, including both operable and not-operable non-small cell lung cancer. Age, occupation, type of health insurance, clinical TNM, central location, diagnostic method and therapeutic regimen were used to construct nomogram.[33] We propose herein sex-specific prognostic scores in a western population, assessed a significantly larger population and took into account a larger number of parameters.

performance status 2 (5 points), ASA score 2 (4 points) and undergoing pneumonectomy (5 points) receives a total score of 56 points. The corresponding predicted 1, 3 and 5-year survival probabilities are 91.4%, 79.7% and 71.9%, respectively, to be read on the blue, red and green curves on the panel a of the figure.

Stage	Beta coefficient (SE)	C index
IA	1.27 (0.077)	0.688
IB	1.12 (0.11)	0.653
IIA	1.39 (0.23)	0.632
IIB	0.94 (0.10)	0.617
IIIA	1.05 (0.083)	0.634
IIIB-C	0.98 (0.15)	0.647
IV	1.31 (0.16)	0.668

Estimates are pooled over imputed datasets. A perfect calibration of the model should yield a beta coefficient of 1.

Table 3: **Regression coefficient and *c* index of the model in the temporal validation set stratified by post-operative stage.**

Prediction of survival is of paramount importance in cancer patients; the potential utility is even higher after complete resection of disease to guide subsequent management in terms of follow-up rules and/or adjuvant treatments.[30] Adjuvant chemotherapy continues to represent the standard of care in patients with stage II-III disease, on the basis of several randomized trials and metanalysis.[53–58] However, the gain of survival at 5-years is estimated at approximately 5%, raising the question of exposing a large number of patients to potentially harmful treatments, with only a minority of them experiencing a benefit.[57] In stage I disease, post-hoc analysis showed that the benefit of adjuvant chemotherapy is limited to patients whose tumor diameter is >4 cm, this measure representing a cut-off to propose post-operative chemotherapy in this subset of stage I disease, with the same limitation than in stage II-III.[59] To date, other tumor related parameters, including histology or grade, presence of emboli or aerogenous spread, although recognized as impacting survival, are not taken into account in guidelines to prescribe adjuvant therapies.[7–10] Of note emboli and aerogenous spread are assessed heterogeneously and great variation is reported in terms of percentage of occurrence in different population of resectable lung cancer.[9,10] In the era of targeted treatments, immunotherapies, and combined treatments, the importance of identifying patients at increased risk of recurrence (and, as a consequence, of impaired survival) is even stronger, as these treatments are potentially more efficacious, but may have significant toxicities, have certainly important costs, and may require long-lasting administration periods.[11,60–62]

We choose for development and temporal validation sets specific time frames, i.e., up to December 2016 for development set and beginning January the 1st 2017 for validation set, respectively, as novel systemic treatments (in the setting of non-resectable recurrence or metastatic relapse after surgery) became widely available in France at the end of 2016. We think that our choice allowed showing consistency of our prognostic score and nomograms, regardless of type of treatment in case of relapse.

We developed two nomograms, for male and female patients, respectively. Pathophysiology of disease is different according to sex, and impact of treatments, including surgery, are different in men and women, as outlined in our recent nation-wide experience.[5] Our study outlined the predictive value of some other host-related factors, including age, comorbidities, BMI, WHO performance status, GOLD or ASA score, underlying the concept of the strong intervention of host factors –in particular those related to fitness-in determining the outcome of cancer.[5,21] In the present work we confirmed the positive prognostic impact of increasing BMI, in agreement with our previous reports based on nation-wide or institutional series.[5,24,25] Differently from most other cancers, overweight and obesity affect favorably short and long-term outcome of resectable NSCLC, as compared to normal-weight, underweight representing, on the other hand, a strong negative prognostic factor: this is the so-called lung cancer paradox.[5] In resectable lung cancer, BMI is positively correlated with psoas or total abdominal muscular area as well as with total muscular mass, measured by CT scan or extrapolated by anthropometric measures.[24,25] We also showed that in patients undergoing pneumonectomy for NSCLC, BMI is inversely correlated with plasma C-reactive protein levels, a marker of systemic inflammation in turn associated to tumor burden, whereas it is directly correlated with number of antigen-presenting dendritic cells in tumor immune microenvironment.[23] These associations underline the complex interplay between host and tumor, whose interface is probably represented by the tumor immune microenvironment.[23]

Thus, our score could include both host and tumor related factors, underlying the concept that both should be taken into account in the clinical decision-making. When looking at algorithms more frequently employed in lung cancer management, decisions are almost exclusively based on disease features (stage), and in the setting of resectable lung cancer, patient fitness is taken into account only to confirm that an individual will be able to face possible side effects of treatments.[5,37] Similarly, precision medicine in the setting of lung cancer management is mainly based on molecular features (i.e., presence of driver oncogene activating mutation, or expression of immune check point molecules).[11] While waiting development of truly personalized approaches, identifying a limited number of parameters allowing establishing risk groups of patients with resectable NSCLC may allow planning of trials of interventions or follow-up strategies.

Our study has two main limitations: firstly, differently from induction, adjuvant treatments are not collected in the Epithor database, because these treatments are performed under the care of referring pneumologists, often in centers outside the hospitals with thoracic surgery facilities. However, our goal being identifying patients with poor long-term outcome after standard treatments, and, specifically, surgery, we built

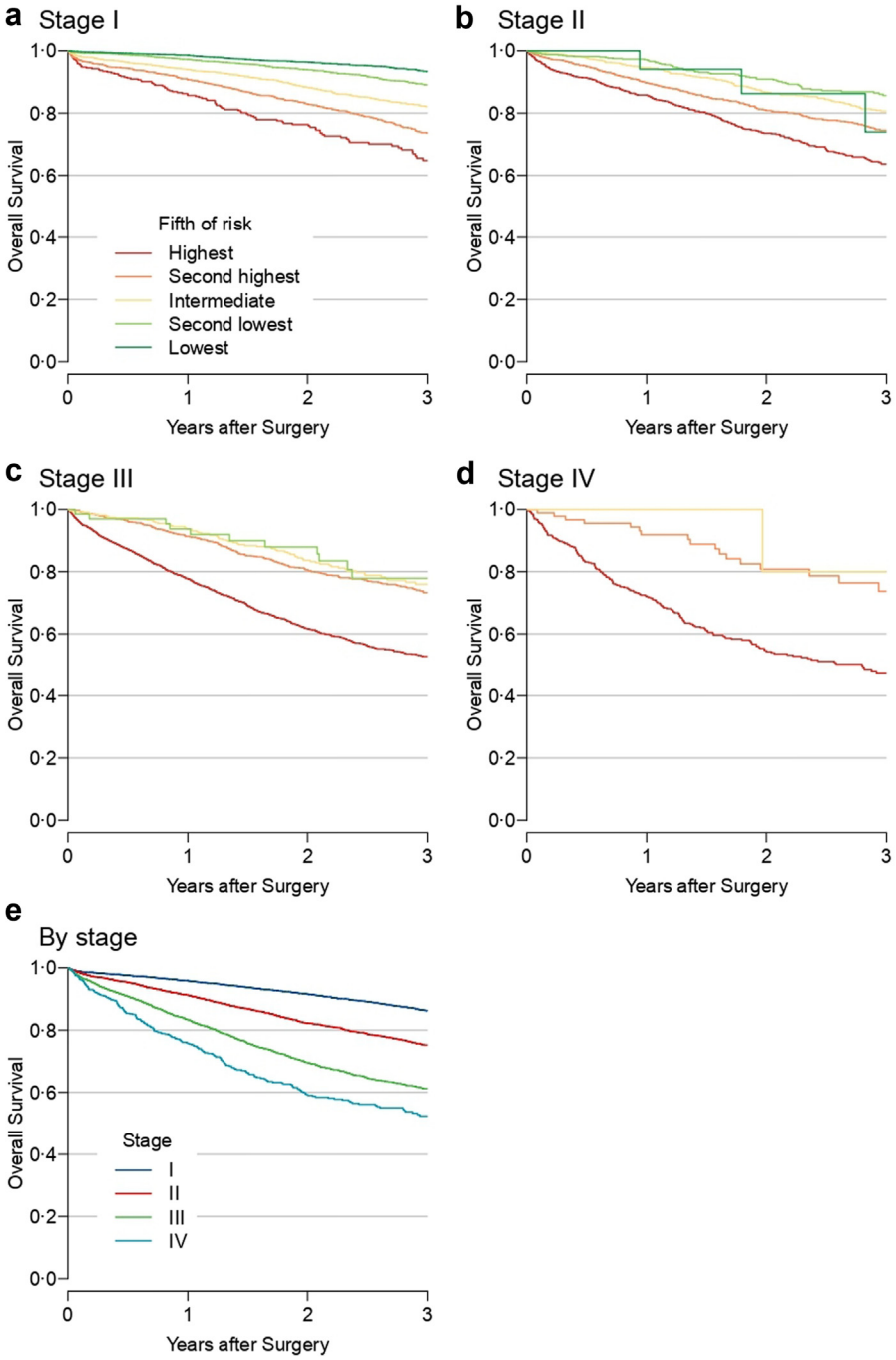

***Fig. 4:* Survival by fifths of score according to post-operative stage in the temporal validation sets.** Panel a: stage I; panel b: stage II; panel c: stage III; panel d: stage IV. The score was divided into five equal-sized groups in the whole set. Since stage is part of the model, not all score categories can be found in the different stage subsets. For comparison, survival curves by stage of disease in the whole population is shown in panel e.

score and sex-specific nomograms taking into account baseline tumor and host factors, and not chemotherapy, which is anyway prescribed inside MDT according to guidelines, whenever needed. The second limitation is represented by the lack of information on cancer recurrence, only overall survival being be assessed. Anyway, outside clinical trials, information on date of recurrence is often not reliable, because of differences

in follow-up strategies (in times of timing and imaging procedures) from one center to another, possibly leading to significant delay in some centers and an early diagnosis of recurrence in others. Anyway, in an unselected population of lung cancer, long-term deaths are mainly related to cancer specific events.[63] Also, the score predictive ability was good but not excellent, with c statistics about 0.7. It seems that the score failed to capture a reasonably large group of individuals with very high risk. This may be because we missed important predictors of very poor survival, or because it is intrinsically difficult to predict very high risk with pre-surgery variables, for instance because a very high risk at short time after surgery depends on what occurred during surgery or shortly after.

Thus, our score and related nomograms developed for both male and female patients could represent useful, inexpensive, easy to obtain, and reproducible tools. Pending specifically designed studies, they could be employed for clinical decision making, providing reliable information on long-term risk after surgery for resectable NSCLC. Furthermore, they could be useful in development of future trials of personalized perioperative management of resectable lung cancer in terms of perioperative treatments and follow-up strategies. We suggest that our score and nomograms could be used to design trials of perioperative immunotherapy or chemo-immunotherapy including only high-risk patients, as well as trials of perioperative systemic treatments including a whole population of resected lung cancer stratified according to risk categories identified by our tools.

Contributors

M.A.: Conceptualization, investigation, methodology, formal analysis, writing-original draft, supervision, validation. E.D.: conceptualization, data curation, investigation, writing-original draft, validation. L.B., P.E.F., F.L.P.B., P.B.P.: data curation, investigation, validation. P.A.T., M.D.: funding acquisition, data curation, investigation, validation, underlying data verification. R.P.: methodology, formal analysis, writing-original draft, supervision, validation.

Data sharing statement

Data are available after formal request to and acceptance by the French Society of Thoracic and Cardiovascular Surgery.

Declaration of interests

We declare no competing interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanepe.2022.100566.

References

1 Lung cancer statistics. https://www.wcrf.org/cancer-trends/lung-cancer-statistics. Accessed June 6, 2022.
2 Deboever N, Mitchell KG, Feldman HA, et al. Current surgical indications for non-small-cell lung cancer. *Cancers (Basel)*. 2022;14(5):1263. https://doi.org/10.3390/cancers14051263.
3 Postmus PE, Kerr KM, Oudkerk M, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2017;28(suppl_4):iv1–iv21. https://doi.org/10.1093/annonc/mdx222.
4 Detterbeck FC, Lewis SZ, Diekemper R, et al. Executive summary: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2013;143(5 Suppl):7S–37S. https://doi.org/10.1378/chest.12-2377.
5 Alifano M, Daffré E, Iannelli A, et al. The reality of lung cancer paradox: the impact of body mass index on long-term survival of resected lung cancer. A French nationwide analysis from the Epithor database. *Cancers*. 2021;13(18):4574. https://doi.org/10.3390/cancers13184574.
6 Lu C, Bera K, Wang X, et al. A prognostic model for overall survival of patients with early-stage non-small cell lung cancer: a multicentre, retrospective study. *Lancet Digit Health*. 2020;2(11):e594–e606. https://doi.org/10.1016/s2589-7500(20)30225-9.
7 Mansuet-Lupo A, Bobbio A, Blons H, et al. The new histologic classification of lung primary adenocarcinoma subtypes is a reliable prognostic marker and identifies tumors with different mutation status: the experience of a French cohort. *Chest*. 2014;146(3):633–643. https://doi.org/10.1378/chest.13-2499.
8 Sakakura N, Mizuno T, Kuroda H, et al. The eighth TNM classification system for lung cancer: a consideration based on the degree of pleural invasion and involved neighboring structures. *Lung Cancer*. 2018;118:134–138. https://doi.org/10.1016/j.lungcan.2018.02.009.
9 Strano S, Lupo A, Lococo F, et al. Prognostic significance of vascular and lymphatic emboli in resected pulmonary adenocarcinoma. *Ann Thorac Surg*. 2013;95(4):1204–1210. https://doi.org/10.1016/j.athoracsur.2012.12.024.
10 Chen D, Mao Y, Wen J, et al. Tumor spread through air spaces in non-small cell lung cancer: a systematic review and meta-analysis. *Ann Thorac Surg*. 2019;108(3):945–954. https://doi.org/10.1016/j.athoracsur.2019.02.045.
11 Catacchio I, Scattone A, Silvestris N, Mangia A. Immune prophets of lung cancer: the prognostic and predictive landscape of cellular and molecular immune markers. *Transl Oncol*. 2018;11(3):825–835. https://doi.org/10.1016/j.tranon.2018.04.006.
12 Michelotti A, de Scordilli M, Bertoli E, et al. NSCLC as the paradigm of precision medicine at its finest: the rise of new druggable molecular targets for advanced disease. *Int J Mol Sci*. 2022;23(12):6748. https://doi.org/10.3390/ijms23126748.
13 Rivera-Concepcion J, Uprety D, Adjei AA. Challenges in the use of targeted therapies in non-small cell lung cancer. *Cancer Res Treat*. 2022;54(2):315–329. https://doi.org/10.4143/crt.2022.078.
14 Germain C, Gnjatic S, Tamzalit F, et al. Presence of B cells in tertiary lymphoid structures is associated with a protective immunity in patients with lung cancer. *Am J Respir Crit Care Med*. 2014;189(7):832–844. https://doi.org/10.1164/rccm.201309-1611OC.
15 Goc J, Germain C, Vo-Bourgais TK, et al. Dendritic cells in tumor-associated tertiary lymphoid structures signal a Th1 cytotoxic immune contexture and license the positive prognostic value of infiltrating CD8+ T cells. *Cancer Res*. 2014;74(3):705–715. https://doi.org/10.1158/0008-5472.CAN-13-1342.
16 Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med*. 2012;366(26):2443–2454. https://doi.org/10.1056/NEJMoa1200690.
17 Forde PM, Spicer J, Lu S, et al. Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. *N Engl J Med*. 2022;386(21):1973–1985. https://doi.org/10.1056/NEJMoa2202170.
18 Bobbio A, Alifano M. Immune therapy of non-small cell lung cancer. The future. *Pharmacol Res*. 2015;99:217–222. https://doi.org/10.1016/j.phrs.2015.06.011.
19 Muthusamy B, Patil PD, Pennell NA. Perioperative systemic therapy for resectable non-small cell lung cancer. *J Natl Compr Cancer Netw*. 2022;20(8):953–961. https://doi.org/10.6004/jnccn.2022.7021.
20 Icard P, Iannelli A, Lincet H, Alifano M. Sarcopenia in resected non-small cell lung cancer: let's move to patient-directed strategies. *J Thorac Dis*. 2018;10(Suppl 26):S3138–S3142. https://doi.org/10.21037/jtd.2018.08.34.

21 Schussler O, Bobbio A, Dermine H, et al. Twenty-year survival of patients operated on for non-small-cell lung cancer: the impact of tumor stage and patient-related parameters. *Cancers*. 2022;14(4):874. https://doi.org/10.3390/cancers14040874.

22 Alifano M, Falcoz PE, Seegers V, et al. Preresection serum C-reactive protein measurement and survival among patients with resectable non-small cell lung cancer. *J Thorac Cardiovasc Surg*. 2011;142(5):1161–1167. https://doi.org/10.1016/j.jtcvs.2011.07.021.

23 Alifano M, Mansuet-Lupo A, Lococo F, et al. Systemic inflammation, nutritional status and tumor immune microenvironment determine outcome of resected non-small cell lung cancer. *PLoS One*. 2014;9(9):e106914. https://doi.org/10.1371/journal.pone.0106914.

24 Hervochon R, Bobbio A, Guinet C, et al. Body mass index and total psoas area affect outcomes in patients undergoing pneumonectomy for cancer. *Ann Thorac Surg*. 2017;103(1):287–295. https://doi.org/10.1016/j.athoracsur.2016.06.077.

25 Icard P, Schussler O, Loi M, et al. Pre-disease and pre-surgery BMI, weight loss and sarcopenia impact survival of resected lung cancer independently of tumor stage. *Cancers*. 2020;12(2):266. https://doi.org/10.3390/cancers12020266.

26 Thompson D, Perry LA, Renouf J, et al. Prognostic utility of inflammation-based biomarkers, neutrophil-lymphocyte ratio and change in neutrophil-lymphocyte ratio, in surgically resected lung cancers. *Ann Thorac Med*. 2021;16(2):148–155. https://doi.org/10.4103/atm.ATM_382_20.

27 Wang J, Kalhor N, Hu J, et al. Pretreatment neutrophil to lymphocyte ratio is associated with poor survival in patients with stage I-III non-small cell lung cancer. *PLoS One*. 2016;11(10):e0163397. https://doi.org/10.1371/journal.pone.0163397.

28 Trestini I, Gkountakos A, Carbognin L, et al. Muscle derangement and alteration of the nutritional machinery in NSCLC. *Crit Rev Oncol Hematol*. 2019;141:43–53. https://doi.org/10.1016/j.critrevonc.2019.06.007.

29 Sasaki A, Nagatake T, Egami R, et al. Obesity suppresses cell-competition-mediated apical elimination of RasV12-transformed cells from epithelial tissues. *Cell Rep*. 2018;23(4):974–982. https://doi.org/10.1016/j.celrep.2018.03.104.

30 Boudou-Rouquette P, Arrondeau J, Gervais C, et al. Development and validation of a host-dependent, PDL1-independent, biomarker to predict 6-month progression-free survival in metastatic non-small cell lung cancer (mNSCLC) patients treated with anti-PD1 immune checkpoint inhibitors (ICI) in the CERTIM cohort: the ELY study. *eBioMedicine*. 2021;73:103630. https://doi.org/10.1016/j.ebiom.2021.103630.

31 Jouinot A, Ulmann G, Vazeille C, et al. Hypermetabolism is an independent prognostic factor of survival in metastatic non-small cell lung cancer patients. *Clin Nutr*. 2020;39(6):1893–1899. https://doi.org/10.1016/j.clnu.2019.08.003.

32 Liang W, Zhang L, Jiang G, et al. Development and validation of a nomogram for predicting survival in patients with resected non-small-cell lung cancer. *J Clin Oncol*. 2015;33(8):861–869. https://doi.org/10.1200/JCO.2014.56.6661.

33 Xiao HF, Zhang BH, Liao XZ, et al. Development and validation of two prognostic nomograms for predicting survival in patients with non-small cell and small cell lung cancer. *Oncotarget*. 2017;8(38):64303–64316. https://doi.org/10.18632/oncotarget.19791.

34 Pilotto S, Sperduti I, Leuzzi G, et al. Prognostic model for resected squamous cell lung cancer: external multicenter validation and propensity score analysis exploring the impact of adjuvant and neoadjuvant treatment. *J Thorac Oncol*. 2018;13(4):568–575. https://doi.org/10.1016/j.jtho.2017.12.003.

35 Pilotto S, Sperduti I, Novello S, et al. Risk stratification model for resected squamous-cell lung cancer patients according to clinical and pathological factors. *J Thorac Oncol*. 2015;10(9):1341–1348. https://doi.org/10.1097/JTO.0000000000000628.

36 Bria E, Di Modugno F, Sperduti I, et al. Prognostic impact of alternative splicing-derived hMENA isoforms in resected, node-negative, non-small-cell lung cancer. *Oncotarget*. 2014;5(22):11054–11063. https://doi.org/10.18632/oncotarget.2609.

37 Thomas PA, Berbis J, Falcoz PE, et al. National perioperative outcomes of pulmonary lobectomy for cancer: the influence of nutritional status. *Eur J Cardio Thorac Surg*. 2014;45(4):652–659. https://doi.org/10.1093/ejcts/ezt452. discussion 659.

38 Falcoz PE, Conti M, Brouchet L, et al. The Thoracic Surgery Scoring System (Thoracoscore): risk model for in-hospital death in 15,183 patients requiring thoracic surgery. *J Thorac Cardiovasc Surg*. 2007;133(2):325–332. https://doi.org/10.1016/j.jtcvs.2006.09.020.

39 Detterbeck FC, Boffa DJ, Kim AW, Tanoue LT. The eighth edition lung cancer stage classification. *Chest*. 2017;151(1):193–203. https://doi.org/10.1016/j.chest.2016.10.010.

40 French register of deceased persons. https://arbre.app/en/insee. Accessed June 6, 2022.

41 Rubin DB, Schenker N. Multiple imputation in health-care databases: an overview and some applications. *Stat Med*. 1991;10:585–598.

42 White IR, Royston P. Imputing missing covariate values for the Cox model. *Stat Med*. 2009;28:1982–1998.

43 White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med*. 2011;30:377–399.

44 Grambsch P, Therneau T. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika*. 1994;81:515–556.

45 Royston P. A strategy for modelling the effect of a continuous covariate in medicine and epidemiology. *Stat Med*. 2000;19:1831–1847.

46 Vergouwe Y, Royston P, Moons KG, Altman DG. Development and validation of a prediction model with missing predictor data: a practical approach. *J Clin Epidemiol*. 2010;63:205–214.

47 Wood AM, White IR, Royston P. How should variable selection be performed with multiply imputed data? *Stat Med*. 2008;27:3227–3246.

48 Harrell F, Lee K, Mark D. Tutorial in biostatistics multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med*. 1996;15:361–387.

49 Wood AM, Royston P, White IR. The estimation and use of predictions for the assessment of model performance using large samples with multiply imputed data. *Biom J*. 2015;57:614–632.

50 Pencina MJ, D'Agostino RB, Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. *Stat Med*. 2011;30(1):11–21.

51 Uno H, Tian L, Cai T, Kohane IS, Wei LJ. A unified inference procedure for a class of measures to assess improvement in risk prediction systems with survival data. *Stat Med*. 2013;32(14):2430–2442.

52 R Core Team. *R: a language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing; 2013. URL http://www.R-project.org/.

53 Douillard JY, Tribodet H, Aubert D, et al. Adjuvant cisplatin and vinorelbine for completely resected non-small cell lung cancer: subgroup analysis of the lung adjuvant cisplatin evaluation. *J Thorac Oncol*. 2010;5(2):220–228. https://doi.org/10.1097/JTO.0b013e3181c814e7.

54 Burdett S, Pignon JP, Tierney J, et al. Adjuvant chemotherapy for resected early-stage non-small cell lung cancer. *Cochrane Database Syst Rev*. 2015;(3):CD011430. https://doi.org/10.1002/14651858.CD011430.

55 Novello S, Torri V, Grohe C, et al. International Tailored Chemotherapy Adjuvant (ITACA) trial, a phase III multicenter randomized trial comparing adjuvant pharmacogenomic-driven chemotherapy versus standard adjuvant chemotherapy in completely resected stage II-IIIA non-small-cell lung cancer. *Ann Oncol*. 2022;33(1):57–66. https://doi.org/10.1016/j.annonc.2021.09.017.

56 Butts CA, Ding K, Seymour L, et al. Randomized phase III trial of vinorelbine plus cisplatin compared with observation in completely resected stage IB and II non-small-cell lung cancer: updated survival analysis of JBR-10. *J Clin Oncol*. 2010;28(1):29–34. https://doi.org/10.1200/JCO.2009.24.0333.

57 Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. *J Clin Oncol*. 2008;26(21):3552–3559. https://doi.org/10.1200/JCO.2007.13.9030.

58 Bonomi M, Pilotto S, Milella M, et al. Adjuvant chemotherapy for resected non-small-cell lung cancer: future perspectives for clinical research. *J Exp Clin Cancer Res*. 2011;30(1):115. https://doi.org/10.1186/1756-9966-30-115.

59 Strauss GM, Herndon 2nd JE, Maddaus MA, et al. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. *J Clin Oncol*. 2008;26(31):5043–5051. https://doi.org/10.1200/JCO.2008.16.4855.

60 Liu SY, Zhang JT, Zeng KH, Wu YL. Perioperative targeted therapy for oncogene-driven NSCLC. *Lung Cancer*. 2022;172:160–169. https://doi.org/10.1016/j.lungcan.2022.05.007.
61 Felip E, Altorki N, Zhou C, et al. Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial. *Lancet*. 2021;398(10308):1344–1357. https://doi.org/10.1016/S0140-6736(21)02098-5.
62 Wu YL, Tsuboi M, He J, et al. Osimertinib in resected *EGFR*-mutated non-small-cell lung cancer. *N Engl J Med*. 2020;383(18):1711–1723. https://doi.org/10.1056/NEJMoa2027071.
63 Berghmans T, Pasleau F, Paesmans M, et al. Surrogate markers predicting overall survival for lung cancer: ELCWP recommendations. *Eur Respir J*. 2012;39(1):9–28. https://doi.org/10.1183/09031936.00190310.