Risk Stratification Model for Resected Squamous-Cell Lung Cancer Patients According to Clinical and Pathological Factors

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Introduction: The aim of this analysis (AIRC-MFAG project no. 14282) was to define a risk classification for resected squamous-cell lung cancer based on the combination of clinicopathological predictors to provide a practical tool to evaluate patients' prognosis.

Methods: Clinicopathological data were retrospectively correlated to disease-free/cancer-specific/overall survival (DFS/CSS/OS) using a Cox model. Individual patient probability was estimated by logistic equation. A continuous score to identify risk classes was derived according to model ratios and dichotomized according to prognosis with receiver operating characteristic analysis.

Results: Data from 573 patients from five institutions were gathered. Four hundred ninety-four patients were evaluable for clinical analysis (median age: 68 years; male/female: 403/91; T-descriptor according to TNM 7th edition 1–2/3–4: 330/164; nodes 0/>0: 339/155; stages I and II/III and IV: 357/137). At multivariate analysis, age, T-descriptor according to TNM 7th edition, nodes, and grading were independent predictors for DFS and OS; the same factors, except age and grading, predicted CSS. Multivariate model predict individual patient probability with high prognostic accuracy (0.67 for DFS). On the basis of receiver operating characteristic-derived cutoff, a two-class model significantly differentiated low-risk and high-risk patients for 3-year DFS (64.6% and 32.4%, $p < 0.0001$), CSS (84.4% and 44.5%, $p < 0.0001$), and OS (77.3% and 38.8%, $p < 0.0001$). A three-class model separated low-risk, intermediate-risk, and high-risk patients for 3-year DFS (64.6%, 39.8%, and 21.8%, $p < 0.0001$), CSS (84.4%, 55.4%, and 30.9%, $p < 0.0001$), and OS (77.3%, 47.9%, and 27.2%, $p < 0.0001$).

Conclusions: A risk stratification model including often adopted clinicopathological parameters accurately separates resected squamous-cell lung cancer patients into different risk classes. The project is currently ongoing to integrate the clinicopathological model with investigational molecular predictors.

Key Words: Squamous lung cancer, Prognosis, Prognostic model, Clinicopathological predictors.

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Despite the major advances in the personalized treatment of non–small-cell lung cancer (NSCLC), effective targeted therapies for the squamous lung cancer subtype (SQLC, approximately the 25% of NSCLC) still lack. Particularly, in the context of adenocarcinoma, reliable evidences are available suggesting that cancer development and progression may be addicted through aberrant pathways specifically triggered by genetic abnormalities, constitutively acting as oncogenic drivers. Emblematic examples of such dependency are represented by *EGFR* mutant[1–3] and *ALK* positive adenocarcinoma,[4] whereas the treatment with their specific tyrosine kinase inhibitors significantly contribute to improve prognosis, disease control, symptoms, and quality of life when compared with traditional chemotherapy.

Besides these major advances for adenocarcinoma, SQLC still requires the identification and validation of a reliable clinicopathological and molecular portrait, to better stratify SQLC patients according to prognosis and to predict their potential susceptibility to specific targeted treatments.

Regarding candidate clinicopathological factors, the tumor, node, metastasis (TNM) stage represents the most

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reliable prognostic predictor in NSCLC patients.[5] In addition to the TNM staging, the prognostic significance of the predominant histologic patterns has been validated in lung adenocarcinoma, whereas any similar prognostic role has been observed for histological subtyping of SQLC (ie, keratinizing, nonkeratinizing, basaloid, and clear cell subtypes).[6,7] However, in this uncertain landscape, several investigated pathological factors (including single cell invasion, tumor budding, nuclear diameter, number of metastatic lymph nodes, lymphatic/vascular and pleural invasion) demonstrated a potential prognostic role in different series of resected SQLC (R-SQLC), retrospectively analyzed.[8–10]

With regard to molecular abnormalities, the Cancer Genome Atlas Research Project recently published the largest genomic characterization of SQLC, providing a comprehensive landscape of genomic and epigenomic alterations featuring the early stage of the disease. This study validated the existence of potentially druggable genes or pathways and provided the first in vivo evidence of the mutual exclusivity of genomic alterations.[11]

The general aim of our project was to create a prognostic nomogram for R-SQLC on the basis of validated and putative biomarkers, which may directly determine patient predictions, risk stratification, and treatment assignment with targeted agents, according to the emerged findings in the preclinical setting. This strategy, may thus successfully integrate the known clinical findings with the newest genetic acquisitions into prognostic (and hopefully) predictive nomograms. In this regard, a risk classification for R-SQLC according to the combination of clinicopathological predictors has been accomplished, to identify the best and worst prognostic performers.

MATERIALS AND METHODS

A step-by-step protocol was followed according to the methodological approach for building a nomogram for cancer prognosis proposed by Iasonos et al.[12] with respect to the Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK) criteria for the conduction of a retrospective study in the context of an unselected population.[13,14]

Patients' Population

R-SQLC cases with stored tissue available for biomolecular analyses with at least 2 years of follow-up from the removal of the primary tumor, who underwent surgery since 2009 in five Italian institutions (University of Verona; Regina Elena National Cancer Institute, Rome; University of Torino; University of Perugia; University-Foundation of Chieti), were considered eligible. A merged database of data was accomplished. Pathological diagnosis was made according to the World Health Organization classification and the American Joint Committee on Cancer; the Union for International Cancer Control TNM system (7th edition) for lung cancer was applied for disease staging.

End Points

The aim of this analysis (Italian Association for Cancer Research, AIRC, first step of the MFAG project no. 14282) was to develop and validate a clinicopathological prognostic risk-class model to identify the best and worst performers in the context of a multicenter population of R-SQLC. The model was developed on the basis of a multivariate analysis exploring the independent impact of clinicopathological factors on overall survival (OS, time between diagnosis and death for any cause), cancer-specific survival (CSS, time between diagnosis and death due to cancer progression), and disease-free survival (DFS, time between diagnosis and local/distant recurrence, onset of secondary cancer or death for any cause).

Statistical Analysis

Descriptive statistics was used to summarize pertinent study information. Follow-up was analyzed and reported according to Shuster.[15] Associations between variables were analyzed according to the Pearson χ^2 test. The hazard ratio (HR) and the 95% confidence intervals (95% CI) were estimated using the Cox univariate model.[16] A multivariate proportional hazard model was developed using stepwise regression (forward selection, enter limit and remove limit, $p = 0.10$ and $p = 0.15$, respectively), to identify independent predictors of outcomes. The assessment of interactions between significant investigational variables was taken into account when developing the multivariate model. In presence of nonlinear distribution of ratios of continuous variables, the receiver operating characteristic (ROC) curve analysis was adopted for dichotomization according to the three outcomes (OS, CSS, and DFS).[17,18] The ROC curve analysis allowed to estimate the area under the curve (AUC) with standard error (SE) and 95% CI, to provide a list of sensitivity, specificity, likelihood ratios, and positive and negative predictive values for all possible threshold values and to calculate the difference between the areas under the ROC curves, with SE, 95% CI and p value.[19] OS, CSS, and DFS were calculated by the Kaplan–Meier product limit method from the date of the surgery until relapse, death due to cancer, and/or death for any cause. Curves were reported for those prognostic factors that resulted independent at the multivariate analysis. The log-rank test was used to assess differences between subgroups. Significance was defined at the p less than 0.05 level. The SPSS (version 18.0; SPSS, Inc., Chicago, IL), R (version 2.6.1; R Foundation for Statistical Computing, Vienna, Austria), and MedCalc (version 14.2.1; MedCalc software, Ostend, Belgium) licensed statistical programs were used for all analyses.

Prognostic Score Assessment

The log-HR obtained from the Cox model was used to derive weighting factors of a continuous prognostic index, aimed to identify differential outcomes' risks. Coefficients estimates were "normalized" dividing by the smallest one and rounding the resulting ratios to the nearest integer value.[20] Thus, a continuous score assigning to patients an "individualized" risk was generated. Two different methods were adopted to derive risk classes[21]: (i) for model A, the score was dichotomized according to prognosis with the ROC analysis (the best "splitter" cutoff is determined)[17]; (ii) for model B, patients' outcomes (OS, CSS, and DFS) were displayed by dividing patients into three risk classes, by considering cutoffs chosen at approximately equal distance along the range of values.[20]

Internal Validation Analysis

To address the multivariate model overfit and to validate the results, a cross-validation technique, which evaluates

the replication stability of the final Cox multivariate model in predicting all outcomes, was also investigated, using a resampling procedure.[12,22,23] This technique generates a number of simulation datasets (at least 100, each approximately 80% of the original size), by randomly selecting patients from the original sample, to establish the consistency of the model across less-powered patient' samples. Risk classes was generated on the basis of the combination of the found risk factors. The ROC analysis allowed to assess the predictive accuracy of the prognostic model, by the AUC determination.[19]

The Harrell's guidelines for the identification of the correct number of covariates were taken into account for the power analysis (the number of deaths should have be more than 10 times greater than the number of investigated predictors, so that the expected error from the Cox model would be less than 10%).[24]

The whole project (AIRC-MFAG Project 14282) was approved by the local Ethics Committee.

RESULTS

Patients

Data from 573 patients from five different Italian institutions were gathered. Four hundred ninety-four patients were evaluable for the clinical analysis, with an attrition rate of 13.7% (the clinical or pathological descriptors for survival analysis were missing in 79 patients). Median age was 68 years (range, 32–83 years). According to a previous model indicating the independent role of the overall number of the resected nodes (with the cutoff of 10) in determining the prognosis of such patients, this parameter was considered for the survival analysis in the univariate and multivariate models.[18] As a clinical descriptor, the median number of resected nodes was 13 (range, 1–62). The adopted T-factor status (T-descriptor according to TNM 7th edition) incorporates all the pertinent T-descriptors (tumor size, status of pleural invasion, or intrapulmonary metastasis). Overall patients' characteristics are shown in Table 1.

TABLE 1. Patients' Characteristics (494 Evaluable Patients for the Clinical Analysis)

	Patients Number (%)
Gender	
Male	403 (81.6)
Female	91 (18.4)
T descriptor according to TNM 7th edition	
1	132 (26.7)
2	227 (46.0)
3	106 (21.6)
4	29 (5.7)
TNM staging	
I	259 (52.4)
II	118 (23.9)
III	102 (19.4)
IV	15 (2.4)
Lymph nodes	
Negative	339 (68.6)
Positive	155 (31.4)
Resected lymph nodes	
<10	133 (26.9)
≥10	361 (73.1)
N status (N descriptor according to TNM 7th edition)	
0	339 (68.6)
1	65 (13.2)
2	63 (12.8)
3	27 (5.4)
Grading	
G 1–2	219 (44.3)
G 3	177 (35.9)
Unknown	98 (19.8)
Chemotherapy	
Neoadjuvant	26 (5.2)
Adjuvant	75 (15.2)
None	272 (55.1)
Unknown	121 (24.5)
Surgery	
Lobectomy	308 (62.3)
Bilobectomy	45 (9.1)
Pneumonectomy	74 (15.0)
Unknown	67 (13.6)

Survival Analysis

Median follow-up was 28 months (range, 1–213 months, 53 months if calculated with the reverse method).[25] The overall number of deaths was 202 (164 due to cancer, 38 due to other causes). Median DFS, CSS, and OS were 38 months (95% CI: 31–45), 81 months (95% CI: 50–112), and 58 months (95% CI: 42–74), with a 5-year rate of 38.6%, 55.8%, and 48.6%, respectively. At the multivariate analysis, age 68 years or younger, T-descriptor according to TNM 7th edition 1–2, negative nodes, and grading 1–2 were significant independent predictors for longer DFS and OS. With regard to CSS, T-descriptor according to TNM 7th edition 1–2 and negative nodes were significant prognostic predictors (Table 2; Supplementary Fig. 1–3, Supplemental Digital Content, http://links.lww.com/JTO/A858).

Internal Validation Analysis

At the cross-validation analysis, nodes, grading, T-descriptor according to TNM 7th edition, and age were confirmed as independent factors for DFS (replication rate: 98%, 72%, 70%, and 86%, respectively). The same factors were confirmed to be independent predictors for OS at the internal validation (replication rate: 100%, 98%, 100%, and 100% for nodes, grading, T-descriptor, and age, respectively). For what concerns CSS, at the cross-validation analysis nodes and T-descriptor were confirmed as independent predictors (replication rate: 93% and 93%, respectively).

Prognostic Score and Model Performance

According to the HRs obtained at the multivariate analysis, a prognostic scoring index was assigned to each patient to identify the individual risk of recurrence (Table 3).

TABLE 2. Survival Analysis

	Disease-Free Survival						Cancer-Specific Survival						Overall Survival					
	Univariate Analysis			Multivariate Analysis			Univariate Analysis			Multivariate Analysis			Univariate Analysis			Multivariate Analysis		
Variables	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Gender (male vs. female)	1.27	0.90–1.79	*0.15*	—	—	—	1.51	0.94–2.42	*0.08*	—	—	—	1.31	0.88–1.96	*0.17*	—	—	—
Age (>68 vs. ≤68 yr)	1.28	1.01–1.63	*0.04*	1.58	1.14–2.18	*0.005*	1.13	0.83–1.55	*0.41*	—	—	—	1.54	1.16–2.04	*0.002*	2.17	1.48–3.17	*<0.0001*
T descriptor according to TNM 7th edition (3–4 vs. 1–2)	2.24	1.73–2.92	*<0.0001*	1.75	1.22–2.51	*0.002*	2.83	2.06–3.90	*<0.0001*	2.26	1.40–3.66	*0.001*	2.69	2.01–3.59	*<0.0001*	2.12	1.40–3.21	*<0.0001*
Lymph nodes (positive vs. negative)	2.23	1.73–2.87	*<0.0001*	2.27	1.57–3.27	*<0.0001*	2.83	2.07–3.87	*<0.0001*	2.93	1.79–4.80	*<0.0001*	2.54	1.91–3.37	*<0.0001*	2.59	1.70–3.96	*<0.0001*
Resected lymph nodes (<10 vs. ≥10)	1.09	0.80–1.49	*0.55*	—	—	—	1.03	0.68–1.54	*0.88*	—	—	—	1.04	0.73–1.47	*0.81*	—	—	—
N status (N descriptor according to TNM 7th edition)																		
1 vs. 0	1.57	1.11–2.22	*0.01*	—	—	—	1.91	1.25–2.93	*0.003*	—	—	—	1.64	1.10–2.43	*0.02*	—	—	—
2–3 vs. 0	3.23	2.37–4.38	*<0.0001*	—	—	—	4.14	2.87–5.96	*<0.0001*	—	—	—	3.80	2.73–5.29	*<0.0001*	—	—	—
Grading (3 vs. 1–2)	1.41	1.03–1.95	*0.03*	1.41	1.03–1.94	*0.033*	1.55	1.01–2.83	*0.04*	—	—	—	1.64	1.13–2.38	*0.009*	1.65	1.13–2.40	*0.008*
TNM staging (III/IV vs. I/II)	3.01	2.30–3.93	*<0.0001*	—	—	—	3.94	2.86–5.43	*<0.0001*	—	—	—	3.48	2.60–4.66	*<0.0001*	—	—	—

HR, hazard ratios; CI, confidence intervals.
Italics indicate significance, defined as $P < 0.05$.

TABLE 3. Prognostic Score Assessment According to Disease-Free Survival

	Score Points		
Disease-Free Survival	**0**	**1**	**2**
Age	≤68	>68	—
T-descriptor according to TNM 7th edition	1–2	—	3–4
Lymph nodes	Negative	—	Positive
Grading	1–2	3	—

TNM, tumor, node, metastasis.

The score dichotomization according to outcome, derived from the ROC analysis and the maximally selected log-rank statistics, identified 2 as the optimal cutoff point. According to the two-class model (model A), a statistically significant prognostic difference between patients at low (score ≤2) and high risk (score >2) was determined for both DFS (3-year: 64.6% and 32.4%, $p < 0.0001$; 5-year: 52.5% and 15.1%; $p < 0.0001$), CSS (3-year: 84.4% and 44.5%, $p < 0.0001$; 5-year: 78.8% and 24.5%; $p < 0.0001$), and OS (3-year: 77.3% and 38.8%, $p < 0.0001$; 5-year: 67.6% and 17.0%; $p < 0.0001$; Fig. 1).

On the basis of the outcome, patients were divided into three risk classes, by considering cutoffs chosen at approximately equal distance along the range of values: (1) low risk of recurrence and death: score 0–2 (ie, the best outcome estimate); (2) intermediate risk of recurrence and death: score 3–4; (3) high risk of recurrence and death: score 5–6 (ie, worst outcome estimate). According to the three-class model (model B), a highly significant prognostic difference between patients at low, intermediate, and high risk was found for DFS (3-year: 64.6%, 39.8%, and 21.8%, $p < 0.0001$; 5-year: 52.5%, 23.2%, and 6.2%, $p < 0.0001$), CSS (3-year: 84.4%, 55.4%, and 30.9%, $p < 0.0001$; 5-year: 78.8%, 35.0%, and 15.5%, $p < 0.0001$), and OS (3-year: 77.3%, 47.9%, and 27.2%, $p < 0.0001$; 5-year: 67.6%, 25.4%, and 9.1%, $p < 0.0001$; Fig. 1).

No difference in the prognostic models' performance according to ROC analysis was found. For DFS, the AUC values were 0.65 (SE, 0.03) in model A (two classes) and 0.67 (SE, 0.03) in model B (three classes) with a sensitivity of 0.54 and a specificity of 0.77 for both the models (Fig. 2). The AUC values for OS were 0.72 (SE, 0.04; sensitivity, 0.74; specificity, 0.67) in model A and 0.72 (SE, 0.03; sensitivity, 0.66; specificity, 0.74) in model B. The AUC values for CSS were 0.71 (SE, 0.04; sensitivity, 0.74; specificity, 0.67) in model A and 0.70 (SE, 0.03; sensitivity 0.74; specificity, 0.67) in model B.

DISCUSSION

The results of the analysis reported herein indicate that the combination of a series of simple, known, and easy-to-use clinicopathological factors is able to significantly discriminate the prognosis of patients resected for SQLC. These factors may be combined in a prognostic tool and allow a stratification of patients in two or three risk classes, with a moderately significant prognostic accuracy.[26]

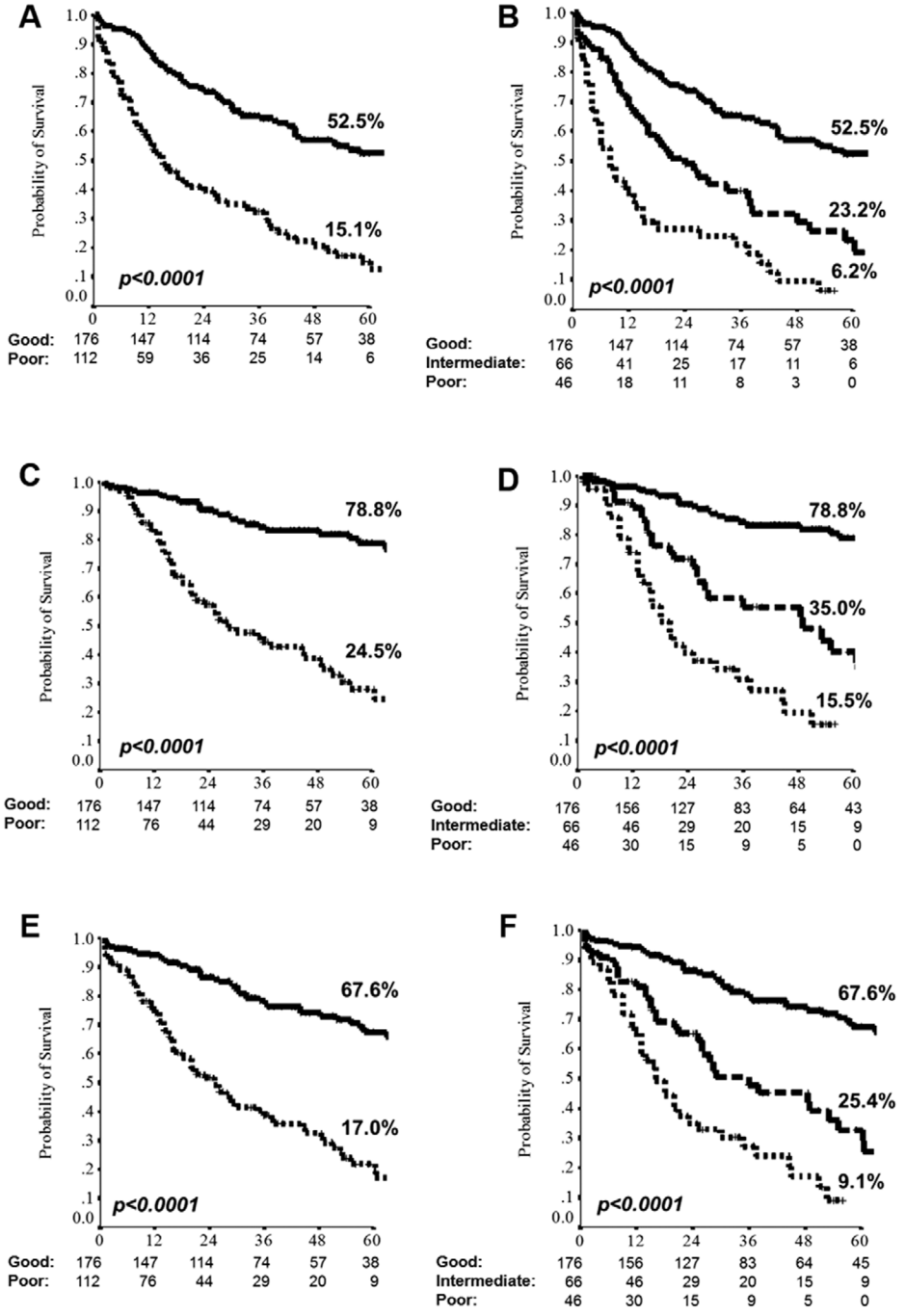

FIGURE 1. Disease-free survival (*A* and *B*), cancer-specific survival (*C* and *D*), and overall survival (*E* and *F*), according to risk classes as developed for model A (*A*, *C*, and *E*) and model B (*B*, *D*, and *F*). The 5-year rate for each outcome is reported, *p* value at long-rank analysis.

These data may help to complement a clinical area, whereas the identification and validation of reliable factors influencing the prognosis of R-SQLC in the context of modern medicine still represent a matter of research. Indeed, although lung cancer represents the most common cause of cancer-related death worldwide and SQLC account for 20% to 30% of NSCLC; nowadays, the pathological stage (TNM) still represents the most reliable prognostic predictor.[5]

Many previous studies have been performed to evaluate various clinicopathological prognostic factors other than the pathological stage for resected NSCLC patients. Age, gender, and T-descriptor according to TNM 7th edition are widely validated predictors, able to significantly contribute to individualized prediction of survival.[27–29]

For that concern lymph nodes status, most studies support the relationship between higher number of examined lymph nodes and better survival.[18,30–32] These results suggest the rationale that the examination of a greater number of lymph nodes in patients with early-stage NSCLC may not only positively affect patients' outcome removing potential metastasized lymph nodes, but also increasing the likelihood of a proper staging and, therefore, of an appropriate therapeutic

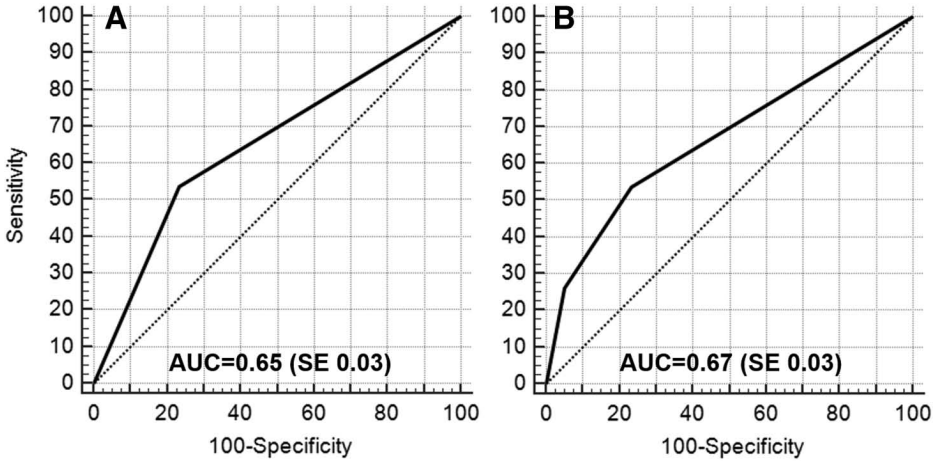

FIGURE 2. Model's prognostic performance of model A (*A*) and model B (*B*) for disease-free survival. AUC, area under the curve; SE, standard error.

approach. In this regard, the number of metastatic nodes (more than the location-based pN stage) seems to be determinant to influence the survival of resected NSCLC patients.[10]

The prognostic significance of different histological patterns, although recognized and validated for lung adenocarcinoma,[6,7] has not been demonstrated in SQLC. In fact, published data on the prognosis of basaloid/nonbasaloid subtypes and according to the degree of keratinization of SQLC, which represent the most investigated pathological factors, are still controversial, and further investigations are required. Kadota et al.[8] retrospectively analyzed a large series of patients with R-SQLC, investigating whether any included pathological factors (tumor differentiation, histologic subtype, tumor nest size, and nuclear grade) correlated with outcomes (OS and DFS), independently of the pathological stage. In multivariate analysis, single cell invasion, nuclear diameter, and tumor budding were independent prognostic predictors of OS, whereas the histologic subtyping did not show prognostic significance. Tumor budding represents a recognized morphological pattern of tumor invasion, identified as an unfavorable prognostic indicator in colorectal cancer, lung adenocarcinoma, and SQLC.[33]

Others recognized predictors of prognosis in the SQLC are represented by the lymphatic invasion[9] and the pathologically proven vascular/pleural invasion that seems to influence both the risk of recurrence and death of SQLC patients,[34] particularly those affected by a peripheral carcinoma.[35]

Tumor grading is a reliable predictor of survival in a broad variety of solid human tumors including lung cancer,[36] and in some cases, such as breast cancer and prostate cancer, its evaluation may influence the main therapeutic approach. Nevertheless, considering that the methods for assessing tumor grading are variables and that this predictor is a composed parameter including a series of additional factors (such as the histopathological subtype, the proportion of the lepidic part, and the nuclear size), the potential biases deriving from the subjective assessment and the interobserver variability among pathologists have to be considered. At this regard, some studies have estimated and evaluated the interobserver variability of grading in lung adenocarcinoma, demonstrating the existence of an high agreement among pathologists for nuclear grading (higher than for histological classifications and the extent of the lepidic pattern), supporting the rationale that this parameter may be currently applicable with acceptable interobserver variability if performed by specifically trained pathologists.[37,38]

Although, as reported, several studies have examined the potential correlation between clinical or pathological markers and survival, to date only one prognostic nomogram, based on the combination of multiple parameters, has been recently validated in resected NSCLC. Liang et al.[39] established and validated the first nomogram for predicting survival of patients with resected NSCLC based on a large database with long-term follow-up. Six independent prognostic factors were identified and included in the prognostic model (age, sex, histology, number of obtained lymph nodes, T category, and N category). The novel nomogram may help clinicians to estimate the survival of resected NSCLC patients and to identify those subgroups of patients more probable to benefit from a specific adjuvant treatment strategy.[39]

In our study, we retrospectively investigated a series of clinicopathological factors with a putative prognostic role in 573 patients undergoing thoracic surgery for a SQLC (494 available for the clinical analysis), to establish their potential value as survival predictors. This risk classification system, comprising the often adopted clinical and pathological parameters (age, T-descriptor according to TNM 7th edition, nodes, and grading), was able to accurately separate R-SQLC patients according to their individual risk of recurrence, death from cancer, and death for any cause, regardless of the adopted method (Fig. 1). As a major finding, our multivariate model was capable to significantly predict the individual risk of recurrence with a moderate prognostic accuracy (0.67). To overcome the potential bias of the retrospective nature of this model, a cross-validation analysis did demonstrate that the independent factors significantly replicate with a high rate.

Once established the accuracy of the model, the extrapolated continuous prognostic score demonstrated to carefully stratify R-SQLC patients in two or three classes (on the basis of the adopted method for the cutoff identification), according to their life expectancy (Table 3). Nevertheless, taking into account the retrospective nature of our data and the potential biases deriving from the analysis of a surgically heterogeneous cohort of patients (gathered from five different institutions),

results should be interpreted cautiously and definitive conclusions should be delayed to the prospective validation of the model. Moreover, the prognostic parameters investigated in this study were not novel compared with previous studies, even though the combinations of these factors were able to significantly discriminate between the prognosis of patients with R-SQLC.

To our knowledge, this is the first prognostic nomogram built selectively for a population of patients affected by the squamous histotype of lung cancer. The recent publication of the first nomogram for predicting survival of patients with resected NSCLC[39] indirectly supports the rationale and the results of our analysis. Indeed, the study of Liang et al.[39] confirmed the reliability of a prognostic nomogram based on some of the same clinicopathological predictors detected in our study (age, T-descriptor, and lymph nodes status).

The ideal perspective is to borrow a patient-centered diagnostic–therapeutic approach in the context of SQLC, analogously of those widely employed for adenocarcinoma. The introduction and validation of a personalized approach may help the clinicians to provide the best available therapy for that specific patient to potentiate the expected clinical benefit and reduce the human and economic cost resulting from a less efficacious not-targeted treatment.

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