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# Prognostic Model for Resected Squamous-Cell Lung Cancer: External Multicenter Validation and Propensity Score Analysis exploring the Impact of Adjuvant and Neoadjuvant Treatment.

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**Conflict of interest statement:**

The authors declare no conflict of interest.

## Abstract

**Introduction.** We developed one of the first clinicopathological prognostic nomograms for resected squamous cell lung cancer (SQLC). Herein, we validate the model in a larger multicenter cohort and we explore the impact of adjuvant/neoadjuvant treatment (ANT).

**Methods.** Resected SQLC patients from January 2002 to December 2012 in six institutions were eligible. To each patient was assigned a prognostic score based on those clinicopathological factors included in the model (age, T-descriptor according to TNM 7th edition, lymph nodes, grading). Kaplan-Meier analysis for disease-free/cancer-specific/overall survival (DFS/CSS/OS) was performed according to three-class risk model. Harrell's C-statistics were adopted for model validation. The effect of ANT was adjusted with propensity score (PS).

**Results.** Data from 1,375 patients was gathered (median age: 68 years; male: 86.8%; T-descriptor 1-2/3-4: 71.7%/24.9%; nodes negative/positive: 53.4%/46.6%; grading 1-2/3: 35.0%/41.1%). Data for survival analysis was available for 1,097 patients. With a median follow-up of 55 months, patients at low risk had a significantly longer DFS *versus* intermediate (HR 1.67, 95% CI 1.40‑2.01) and high risk (HR 2.46, 95% CI 1.90‑3.19), as well as for CSS (HR 2.46, 95% CI 1.80‑3.36; HR 4.30, 95% CI 2.92‑6.33) and OS (HR 1.79, 95% CI 1.48‑2.17; HR 2.33, 95% CI 1.76‑3.07). A trend in favor of ANT was observed for intermediate/high risk patients, particularly for CSS (*p=0.06*; 5-year CSS 72.7% *versus* 60.8%).

**Conclusions.** A model based on a combination of easily available clinicopathological factors effectively stratifies resected SQLC patients in three-risk classes.


**Keywords:** squamous lung cancer, prognosis, nomogram, clinicopathological factors, adjuvant/neoadjuvant treatment.

## Introduction

In recent years, the identification of targetable oncogenic drivers, together with the introduction in clinical practice of a therapeutic decision-making process including tumor genotyping, provided the proof-of-principle that non-small-cell lung cancer (NSCLC) is composed by a group of heterogeneous diseases, which require a personalized approach [1]. Nevertheless, epidemiologically relevant subtypes of NSCLC, as squamous-cell lung cancer (SQLC, approximately 25-30% of NSCLC), still lack of a reliable clinicopathological and molecular characterization, in order to both stratify patients according to their prognosis and predict their potential susceptibility to targeted therapy. The Cancer Genome Atlas Project and similar studies have detected a significant number of genomic and epigenomic alterations in SQLC, some of which are potentially targetable by investigational agents [2, 3]. Nevertheless, only few clinical trials are ongoing to advance the development of targeted therapies in SQLC [4]. Recently, the therapeutic opportunities for lung cancer patients have further expanded with the introduction of immunotherapy, particularly in those tumors that feature a strong genetic diversity, such as SQLC [5]. Although the overexpression of programmed death-ligand 1 (PD-L1) seems to increase the chance to respond to immune checkpoint inhibitors in the advanced disease setting, its prognostic role is still debatable [6].

In this rapidly evolving landscape, the identification of the appropriate risk category for each patient represents a promising strategy for two main reasons [7]. First, in the context of an early stage disease, the prognostic stratification might allow selection of those patients with a more favorable risk-benefit ratio from adjuvant treatments. Second, from an exploratory point-of-view, the molecular characterization of patients featured by a different prognosis, by applying the modern technologies, could help in the identification of those genomic and epigenomic aberrations potentially able to predict the probability of disease recurrence (prognostic factors) and the efficacy of agents selectively targeting these candidate pathways (predictive factors). Applying this research strategy in the field of lung cancer, we designed an effective risk stratification model including commonly adopted clinicopathological parameters (age, T-descriptor according to TNM 7th edition, lymph nodes and grading). This nomogram demonstrated, in a cohort of almost 600 patients, to accurately stratify resected SQLC in risk classes with a mild prognostic accuracy [8]. Nevertheless, to establish if a specific model works satisfactorily, also for patients other than those from whose data it is derived, a validation is mandatory [9]. Therefore, the main objective of this analysis is to validate the already published clinical risk classification model in a larger multicenter series of SQLC patients. Morevoer,

we aim to analyze the impact of adjuvant and neoadjuvant treatment (ANT) in resected SQLC patients both in the overall cohort and in the different risk classes stratified according to the prognostic model, in order to evaluate the clinical applicability of the model in patients' selection and treatment assignment.

## Materials and Methods

### *Patient Population*

Resected SQLC cases with stored tissue available for pathological analysis with at least 2 years of follow-up from the removal of the primary tumor, who underwent surgery from January 2002 to December 2012 in six Italian institutions, were considered eligible. A merged database of data was created. The pathological diagnosis was made according to the World Health Organization classification and the American Joint Committee [10]. In order to be consistent with the previously published prognostic model, the Union for International Cancer Control TNM system ($7^{th}$ edition) for lung cancer was applied for disease staging [11].

### *End Points*

The aim of the clinical part of the project (Italian Association for Cancer Research, AIRC MFAG no. 14282) was to develop ad validate a clinicopathological prognostic risk-class model in order to identify the best and worst performers within a population of resected SQLC. The model was originally created on the basis of a multivariate analysis exploring the independent impact of clinicopathological factors on the selected survival outcomes [8]. Specifically, disease free survival (DFS: time between the date of the surgery and local/distant recurrence, onset of secondary cancer or death for any cause), cancer specific survival (CSS: time between the date of the surgery and death due to cancer progression) and overall survival (OS: time between the date of the surgery and death for any cause). The main aim of this analysis is to validate the already published clinical risk classification model in a larger multicenter series of patients. Morevoer, we aim to analyze the impact of ANT in resected SQLC patients both in the overall cohort and in the different risk classes stratified according the prognostic model.

### *Statistical Analysis*

Descriptive statistics were used to summarize pertinent study information. The reverse method was applied to calculate the median follow-up [12]. Associations between variables were analyzed according to the Pearson Chi-Square test for categorical variables and the t-test for continuous variables. The Hazard Ratio (HR) and the 95% confidence intervals (95% CI) was estimated using the

Cox univariate model. To each patient was assigned a score to classify the individual risk of disease recurrence, based on those clinicopathological factors included in the published prognostic model: age (≤68 *versus* >68 years), T-descriptor according to TNM 7th edition (1-2 *versus* 3-4), lymph nodes (negative *versus* positive) and grading (1-2 *versus* 3). Kaplan-Meier analysis for DFS, CSS and OS was performed according to the published three-class risk model B (low: score 0-2; intermediate: score 3‑4; high: score 5‑6) [8]. The log rank test was adopted to compare the survival curves. The Harrell's C-statistic was adopted to measure the predictive accuracy of the risk model [13]. The effect of adjuvant and neoadjuvant treatment (ANT) was adjusted with the Propensity Score (PS) applying the method of nearest neighbor matching within a specified caliper distance. In this regard, the PS match creates groups of patients with a similar probability to receive the treatment on the basis of their baseline characteristics, in order to minimize the differences in patients' covariates which could become confounding factors in the examination of treatment effects in a non-randomized cohort [14]. Specifically, a PS for the likelihood of receiving ANT was calculated using a covariate adjustment method including a series of clinicopathological factors, which might influence the doctors' choice about treatment: age, T-descriptor according to TNM 7th edition, lymph nodes and grading. According to these covariates, an unmatched sample of patients was identified. By using a 1:1 nearest neighbor matching algorithm that pairs patients with the closest PS within a defined limit (calipers of width equal to 0.2), the PS yielded 2 well-matched patient cohorts (logistic regression estimation algorithm). Significance was defined at the $p<0.05$ level. The SPSS® (18.0), R® (2.6.1), and MedCalc® (14.2.1) licensed statistical programs were used for all analyses. The whole project (AIRC-MFAG Project 14282) was approved by the local Ethics Committee.

## Results

### *Patients*

Data from 1,375 patients from six different Italian institutions was gathered. Median age was 68 years (range, 38-90 years). As a clinical descriptor, the median number of resected nodes was 17 (range, 1-85). Overall patients' characteristics are reported in Table 1. Most of the included patients were male (86.8%), affected by SQLC with T descriptor 1-2 (71.7% *versus* 3-4 24.9%) and stage I-II (71% *versus* III-IV 28.0%). Nearly half of the patients presented lymph nodes involvement (46.3%). The most frequent surgical procedure among the included patients was lobectomy (67.1%), followed by pneumonectomy (24.9%). Overall, 384 patients (27.9%) were treated with adjuvant therapies, including

platinum-based doublet chemotherapy (n = 254, 18.5%), radiotherapy (n = 94, 6.8%) and chemoradiotherapy (n = 36, 2.6%). Two thousand-seventy patients (19.6%) received neoadjuvant treatments, mainly platinum-based doublet chemotherapy (n = 254, 18.5%), with only few cases of radiotherapy (n = 7, 0.5%) and concomitant chemoradiotherapy (n = 9, 0.7%). One hundred-fourteen patients (8.3%) in total received both an adjuvant and a neoadjuvant treatment. According to the previously published prognostic model, 687 patients (50.0%) were classified as low risk (score 0-2), 406 (29.5%) as intermediate risk (score 3-4) and 123 patients (8.9%) as poor risk (score 5-6). Patients' characteristics according to the risk class of the prognostic model (1,216 evaluable patients for the clinical analysis) are reported in Supplementary Table 1.

***Survival Analysis and Validation of the Prognostic Model***

The median follow-up calculated with the reverse method was 55 months (95% CI 51‑59). One thousand ninety-seven patients were evaluable for the survival analysis, with an attrition rate of 21.3% (the clinical or pathological descriptors for survival analysis were missing in 159 patients and the follow-up date were missing in 119 patients). According to the three-class model, patients included in the low risk class had a significantly longer DFS in comparison to patients at intermediate (HR 1.67, 95% CI 1.40‑2.01) and high risk (HR 2.46, 95% CI 1.90‑3.19). The 5-year DFS for low, intermediate and high risk patients was 51.0%, 33.5% and 25.8%, respectively (*p<0.0001*) [Figure 1 - Panel A]. In strict accordance, a statistically significant advantage was observed for low risk patients compared to intermediate and high risk in term of CSS (HR 2.46, 95% CI 1.80‑3.36; HR 4.30, 95% CI 2.92‑6.33) and OS (HR 1.79, 95% CI 1.48‑2.17; HR 2.33, 95% CI 1.76‑3.07). The 5-year CSS for low, intermediate and high risk patients was 82.7%, 64.7% and 53.3%, respectively (p<0.0001). The 5-year OS low, intermediate and high risk patients was 56.7%, 37.9% and 30.9%, respectively (p<0.0001) [Figure 1 - Panel B and C]. C‑statistic was 0.68 (95% CI 0.63‑0.73), 0.66 (95% CI 0.61‑0.71), and 0.68 (95% CI 0.63-0.72) for DFS, CSS and OS, respectively.

***Propensity Score Analysis for the Impact of Adjuvant and Neoadjuvant Treatment***

In the entire patient cohort, no significant differences according to the administration or not of ANT were observed in term of DFS (*p=0.77*; 5-year DFS 44.9% *versus* 42.8%), CSS (*p=0.11*; 5-year CSS 76.2% *versus* 67.4%) and OS (*p=0.16*; 5-year OS 52.0% *versus* 45.9%), when the analysis was corrected by the PS [Figure 2]. Nevertheless, when the overall population was stratified according to the three-class risk model, a trend in favor of ANT was observed for intermediate/high risk patients,

particularly in term of CSS (*p=0.06*; 5-year CSS 72.7% *versus* 60.8%) [Figure 3]. In the low risk group, no significant differences according to the administration or not of ANT were observed in term of any survival outcome analyzed [Supplementary Figure 1].

## Discussion

The results of this multicenter analysis validate in a large cohort of resected SQLC (> 1,300 patients) the prognostic performance of our previously published prognostic index [8]. This model, based on a combination of simple and easily available clinicopathological parameters (age, T-descriptor according to TNM 7th edition, lymph nodes and grading), was able to effectively stratify resected SQLC patients in three risk classes with a mild prognostic accuracy [Figure 1]. Although several prognostic factors included in the nomogram have already been correlated with survival outcomes in lung cancer [15-17], our integrated index represents the one of the first prognostic nomograms built selectively for a population of patients affected by lung cancer with squamous histology. A similar study performed in resected NSCLC (regardless of the histology) by *Liang et al.* contributes to support the reliability of a prognostic model based on clinicopathological predictors [18].

Nevertheless, this analysis presents relevant limitations that need to be acknowledged. First, the retrospective and non-randomized nature of the study limits the interpretation of the results, although the propensity score match helps to minimize the effect of covariates potentially acting as confounders in a non-randomized cohort. Second, the included adjuvant and neoadjuvant treatments were heterogeneous because the analysis was performed over a long period in different institutions. Moreover, data about ANT were unknown for a proportion of patients. Therefore, no definitive conclusions about the applicability of our model in patients' selection for treatment assignment might be drawn.

Among the investigated factors, the prognostic significance of different histological patterns, although recognized and validated for lung adenocarcinoma, is still debatable in SQLC. Two recent studies, based on large retrospective series of surgically resected SQLC, demonstrated the relevance of tumour budding and nest size in grading of SQLC, whereas histological subtyping or nuclear features, such as mitotic rate, did not show any prognostic significance [19, 20].

In addition to the classically investigated factors, the recent advent of immunotherapy led to a growing interest about the potential prognostic and predictive impact of immune-related molecules. A series of heterogeneous and retrospective data is concordant in suggesting the negative prognostic impact of PD-L1 expression in NSCLC, particularly with squamous histology [21-24]. Nevertheless, a recent PD-L1

assessment performed in a large population of early stage NSCLC patients reported that PD-L1 expression is neither prognostic nor predictive of benefit from adjuvant chemotherapy, regardless of the selected cut-off [6]. Globally considered, to date the therapeutical innovations obtained in lung cancer did not translate into a benefit in term of amount of prognostic information available for the clinicians. Therefore, the possibility to use a simple nomogram based on commonly adopted clinicopathological predictors represents an interesting perspective with an easy and immediate applicability.

Another controversial topic in early-stage lung cancer, which might benefit from the availability of a stratification model, is represented by the optimization in the patients' selection for adjuvant/neoadjuvant treatment. In this regard, adjuvant chemotherapy represents the universally accepted standard of care for some patients who underwent surgery for stage II and III NSCLC (and to be considered for stage IB > 4 cm) [25, 26]. Nevertheless, considering that the 5-year OS of patients with resected NSCLC widely varies from 35 to 90% [27] and that the expected survival benefit deriving from adjuvant chemotherapy is modest (approximately 4% of survival improvement at 5 years) [28], the correct identification of those patients more likely to benefit from this treatment is strongly needed. Regarding neoadjuvant treatments, although neoadjuvant chemotherapy has not been evaluated as extensively as adjuvant, it seems to provide a similar benefit in term of OS [29, 30].

Speaking about predictive factors for adjuvant and neoadjuvant treatment, in our analysis, even if no statistically significant advantages were observed for ANT in the three risk classes, the CSS and OS curves visually separate in the intermediate and high risk patients, reaching the threshold for statistically significance [Figure 3]. Moreover, the application of the propensity score analysis, similarly to other relevant study performed in lung cancer [31], strengthens the methodological reliability of our results.

To date, the pathological stage represents the most powerful prognostic factor after lung cancer surgery [27], despite age and performance status crucially contributing to the decision-making process about adjuvant treatments [25]. Recently, the National Comprehensive Cancer Network (NCCN) guidelines included as high risk elements poorly differentiated tumors, vascular and visceral pleural invasion, wedge resection, tumor >4 cm and unknown lymph nodes status [32]. In addition to these pathological factors, a series of molecular biomarkers such as ERCC1, RRM1, BRCA1 and thymidylate synthase (TS) has been investigated. Although the promising impact observed in the context of retrospective analyses, further prospective evaluations failed to demonstrate the predictive applicability of these factors [33-37]. A recent retrospective immunohistochemistry analysis suggested that the concomitant overexpression of β-catenin and cyclin D1 might be associated with poor survival regardless of

platinum-based adjuvant chemotherapy in stage IA-IIA SQLC [38]. Globally considered, to date, no factors (other than histology in advanced setting) have demonstrated to be predictive of benefit or lack of benefit from specific chemotherapeutic agents in NSCLC patients [39]. In the era of molecular profiling, several data has been emerging exploring the role of genomic-based prognostic tools [40, 41] and suggesting their potential superiority over the currently applied clinicopathological criteria in the selection of high risk patients. For example, an internationally validated 14-gene prognostic assay recently was able to predict DFS benefit from ANT in very early stage NSCLC, probably better than those clinicopathological characteristics suggested by the NCCN guidelines [42]. In order to elaborate the huge amount of data nowadays available, a recent large-scale meta-analysis identified, among 42 lung cancer signatures obtained by genome-wide expression profiling analysis, the most promising messenger RNA (mRNA) expression prognostic signatures, appropriate for further validation in prospective clinical studies [43]. In addition, some circulating biomarkers, such as circulating tumor cells and microRNA, might harbor a potential diagnostic, predictive and prognostic significance [44]. Nevertheless, to date, no genetic signatures have demonstrated a reliable clinical value in the context of prospective trials. Moreover, the heterogeneity in term of genes included, platforms applied and type of analyzed tissue strongly limits the applicability of the genomic-based prognostic/predictive models in routinely clinical practice.

In conclusions, although the retrospective and non-randomized nature of this study, the combination of easily available clinicopathological factors into a predictive nomogram might accurately characterize resected SQLC patients according to their prognosis, as effectively validated in the context of an external, large and multicenter cohort. Moreover, the adjuvant/neoadjuvant treatment seems to provide a survival advantage for those patients classified as intermediate and high risk, while the potential benefit for low risk patients appears questionable. Nevertheless, considering the heterogeneity of the included adjuvant and neoadjuvant treatments, no definitive conclusions about the applicability of our model in patients' selection for treatment assignment might be drawn, although our model demonstrated to provide a practical tool to discriminate SQLC patients' prognosis. In this regard, once available a SQLC population stratified in different prognostic groups, the future perspectives include the study of their molecular background in order to identify those immunologic pathways and molecular aberrations potentially able to estimate the probability of disease recurrence. This might lead to the identification of novel biomarkers, whose targeting with specific targeted agents could potentially limit the oncogenic impact and ideally change the natural history of this aggressive disease.

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**Figure 1.**

Disease-free survival (A), cancer-specific survival (B) and overall survival (C) according to the three-class risk model. The 5-year rate for each outcome is reported; *p-value* at long rank analysis.

**Figure 2.**

Disease-free survival (A), cancer-specific survival (B) and overall survival (C) according to the administration or not of adjuvant and neoadjuvant treatment (ANT) in the overall population, adjusted for propensity score analysis. The 5-year rate for each outcome is reported; *p-value* at long rank analysis.

**Figure 3.**

Disease-free survival (A), cancer-specific survival (B) and overall survival (C) according to the administration or not of adjuvant and neoadjuvant treatment (ANT) in the intermediate/high risk population, adjusted for propensity score analysis. The 5-year rate for each outcome is reported; *p-value* at long rank analysis.

**Supplementary Figure 1.**

Disease-free survival (A), cancer-specific survival (B) and overall survival (C) according to the administration or not of adjuvant and neoadjuvant treatment (ANT) in the low risk population, adjusted for propensity score analysis. The 5-year rate for each outcome is reported; *p-value* at long rank analysis.

**Table 1.** Patients' characteristics (1,375 evaluable patients for the clinical analysis).

| | **Patients Number (%)** |
|---|---|
| Median age (range) | 68 (38-90) |
| Gender | |
| *Male* | 1194 (86.8) |
| *Female* | 181 (13.2) |
| Tumor size<br>[T descriptor according to TNM 7th edition] | |
| *0* | 22 (1.6) |
| *1* | 300 (21.8) |
| *2* | 686 (49.9) |
| *3* | 255 (18.5) |
| *4* | 88 (6.4) |
| *Unknown* | 24 (1.7) |
| TNM staging | |
| *I* | 555 (40.4) |
| *II* | 421 (30.6) |
| *III* | 376 (27.3) |
| *IV* | 9 (0.7) |
| *Unknown* | 14 (1.0) |
| Lymph nodes | |
| *Negative* | 728 (52.9) |
| *Positive* | 636 (46.3) |
| *Unknown* | 11 (0.8) |
| Resected lymph nodes | |
| *< 10* | 272 (19.8) |
| *≥ 10* | 877 (63.8) |
| *Unknown* | 226 (16.4) |
| N status<br>[N descriptor according to TNM 7th edition] | |
| *0* | 728 (52.9) |
| *1* | 408 (29.7) |
| *2* | 227 (16.5) |
| *3* | 1 (0.1) |
| *Unknown* | 11 (0.8) |
| Grading | |
| *1-2* | 481 (35.0) |
| *3* | 565 (41.1) |
| *Unknown* | 329 (23.9) |
| Risk Class<br>[according to the prognostic model] | |
| *0-2* | 687 (50.0) |
| *3-4* | 406 (29.5) |
| *5-6* | 123 (8.9) |
| *Unknown* | 159 (11.6) |
| Neoadjuvant Therapy | |
| *No* | 934 (67.9) |
| *Chemotherapy* | 254 (18.5) |
| *Chemoradiotherapy* | 9 (0.7) |
| *Radiotherapy* | 7 (0.5) |
| *Unknown* | 171 (12.4) |
| Surgery | |
| *Lobectomy* | 923 (67.1) |
| *Bi-lobectomy* | 110 (8.0) |
| *Pneumonectomy* | 342 (24.9) |

| | |
|---|---|
| Adjuvant Therapy | |
| *No* | 728 (52.9) |
| *Chemotherapy* | 254 (18.5) |
| *Chemoradiotherapy* | 36 (2.6) |
| *Radiotherapy* | 94 (6.8) |
| *Unknown* | 263 (19.1) |

**Legend - Table 1.** TNM, tumor, node, metastasis.