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HISTOLOGICAL VARIANTS OF LUNG CARCINOMA AND THEIR CLINICAL CORRELATES: A PULMONOLOGY-PATHOLOGY INTEGRATION

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Abstract

Proper histological subtyping of lung cancer is required in prognosis, biomarker evaluation and treatment choice, particularly when tiny biopsies and cytological information are used to base the diagnosis. An analytic methodology of quantitative, retrospective observations evaluated patients with pathologically confirmed primary lung cancer that were adult. Getting clinical, radiology, sampling and pathological features into the pulmonology-pathology workflow. We applied histomorphology and in cases where necessary immunohistochemistry (IHC) to subtype them. Then we employed bivariate testing and multivariate regression to examine the relationship between these subtypes and clinical correlates. The most prevalent type of cancer was adenocarcinoma that constituted 55.1 percent of the cases. The next were squamous cell carcinoma which comprised 22.1% of the cases. Small cell lung carcinoma constituted 17.9% of the cases and other/rare NSCLC constituted 4.8% cases. Scientifically, SCC had a greater smoking background (88.4) and a more notable central tumor (73.9) compared to adenocarcinoma (73.3 and 27.3, respectively). The images showed correlations that showed a greater prevalence of cavitation in SCC (24.6) than in adenocarcinoma (9.9). IHC profiles were fairly effective in distinguishing the various types. As an illustration, TTF-1 and Napsin A were more prevalent in adenocarcinoma (77.9% and 73.3%), in contrast to p40 and p63, which were more prevalent in SCC (85.5% and 81.2%). SCLC was positive in synaptophysin (92.9%), chromogranin (78.6%), and Ki-67 (87.5%). The stage of the case was advanced, and stage IV constituted the greatest prevalence of SCLC (66.1%). When the multivariate model (SCC vs adenocarcinoma) was adopted, p40 positivity (adjusted OR 9.50), smoking (adjusted OR 2.90) and central position (adjusted OR 2.20) were independent predictors in favour of SCC whereas TTF-1 positivity was in favour of adenocarcinoma (adjusted OR 0.10). By integrating the data about pulmonology sampling with the pathology-grounded histomorphology and a specific panel of IHC, it is feasible to do a correct subtyping of lung cancer, as well as to identify a range of clinically relevant associations that are relevant to staging and further biomarker-based therapy approaches.

Keywords: Lung carcinoma, Histological variants, Adenocarcinoma, Squamous cell carcinoma, Small cell lung carcinoma, Immunohistochemistry, Pulmonology–pathology integration.

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INTRODUCTION

Epidemiological problem of lung cancer continues to occupy the main positions on the international agenda; it is the primary cause of cancer-related deaths in the world (Sasaki et al., 2024). It might have been better, but it is the most widespread type of cancer, thus, one must correctly provide the histological subtypes to arrange effective treatments (Siddique et al., 2024). The 2015 system of the lung tumor differentiation offered by the World Health Organization offers a universal framework of differentiation of lung tumors including the primary histological type of lung cancer as adenocarcinoma, squamous cell carcinoma, small cell carcinoma, and large cell carcinoma (Dınız et al., 2017, p. 3). It surpasses the past categorizations and proves that molecular pathology is gradually becoming a better-known concept and can be the foundation of creating specific therapeutics (Inamura, 2017, p. 1). The discovering of these different histological types is quite important in the act of making predictions and choosing treatment especially as the adenocarcinomas are increasingly becoming more common and at the same time squamous cell carcinoma and small cell lung cancer are becoming less common (Dınız et al., 2017, p. 2). This makes it even more important to assure the appropriate diagnosis when using small biopsy and cytology specimens, when it is all the more relevant to distinguish the adenocarcinoma among other non-small cell lung cancers to carry out the molecular testing (Zheng, 2016). Recent changes, in particular, the ones by the International Association of the Study of Lung Cancer, the American Thoracic Society, and European respiratory society, further subclassify adenocarcinoma by histology, pathogenesis, and clinical behavior, becoming much more accurate in such a diagnosis in small samples (Adile, 2024, p. 2293). This high specificity of subclassification is further increased by the fact the diagnoses of large cell carcinoma is becoming less common. To a considerable degree, this is due to the fact that it has been facilitated by the fact that the non-small cell lung cancers are no longer well differentiated via the improved ancillary methods like immunohistochemistry with which it is now more easily categorized (Beasley et al., 2016, p. 238; Pisano et al., 2022). It is a mixed diagnostic modality wherein the histomorphology is enhanced with molecular characterization that is essential to complementary patient care and forecasting patient prognosis in an age of personalized medicine (Dıniz et al., 2017, p. 2). Close collaboration between pulmonologists and pathologists will be required to avail the best diagnostic and treatment opportunities to the patients in a bid to obtain a profound interpretation of the histological variations and their clinical implications (Balraam et al., 2019, p. 191). The last pathology including the ones of the International Association to Study Lung Cancer, the American Thoracic Society, and the European Respiratory Society could streamline the diagnostic process considerably because the special stains and immunostains can be used to divide the histomorphologically unclear cases into adenocarcinoma or squamous cell carcinoma even in small biopsies and cytological samples (Balraam et al., 2019, p. 193). To distinguish between different types of non-small cell lung cancer, including adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, each of which is characterized by a distinctive clinical phenotype and response to treatment, such diagnostic capability is necessary (Fecikova et al., 2024, p. 124; Liang and Xu, 2023). The given subclassification is particularly significant when narrowing down to the context of increased application of small diagnostic samples since the proper distinction between adenocarcinoma and squamous cell carcinoma might play a critical role in making treatment decisions, particularly when it comes to the novel targeted therapy (Balraam et al., 2019, p. 194; Távora et al., 2023, p. 10). To demonstrate the point, a diagnosis of NSCLC without further clearance is no longer deemed adequate in comparison with a definite histologic diagnosis, as today there are definite targeted therapies, which are premised on very specific cell typing (Alessandrini et al., 2018, p. 414). With the introduction of the immunohistochemistry and molecular diagnostics, the classification of non-small cell lung cancer has shifted to further subtype even with the small fragments of tissues (Domagała-Kulawik, 2019, p. 2). The fact that it has been developed especially is important because it is still hard to isolate subtypes especially in minimally differentiated carcinomas. Another potentially possible area is whole slide image computational pathology and deep learning (Abbaker et al., 2024, p. 2). These improved computation methods utilize the parameters that are not perceivable by the human eye, and thus, increase the quality and efficiency of diagnosis to identify non-observable histological differences (Abbaker et al., 2024, p. 2). This approach can help to improve a diagnosis accuracy and contribute to the formation of particular molecular targets, which will be important to create a personalized treatment plan when dealing with non-small cell lung cancer (Balraam et al., 2019, p. 194). The presence of a small immunohistochemistry panel, such as CK7, TTF-1, and p63, has simplified the process of distinguishing between adenocarcinoma and squamous cell carcinoma significantly even in the situation when the cancer was first suspected to be the case of NSCLC-not otherwise specified (Balraam et al., 2019, p. 191; Funkhouser et al., 2018, p. 10). It is a strategic immunohistochemical marker test with the capability of tumor subtyping more than 90 percent accuracy, even poor tumors, and consistent with the demands of a useful antibody panel to characterize cell type non-small cell lung cancer (Brainard & Farver, 2018, p. 17).

METHODOLOGY

Study design and location

The quantitative, observational method, which will be the analytic methodology to be applied in this research, will be used to establish the correlation between histological changes of the lung cancer and clinically relevant variables in an integrated workflow of a pulmonology-pathology unit. One or more tertiary-care hospitals that conduct regular bronchoscopy, CT-guided biopsies, cytology and oncologic staging will be involved in a retrospective cross-sectional study with the outcome follow-up (where possible). Figure 1 gives a brief description of the methodological approach.

Eligibility, population and sample of the study.

The target will be adult patients (18 years and above) whose primary lung cancer was detected by a pathological method either on small biopsy tissues, cytology cell block or resection tissue within the time frame of the given research (e.g. 24-36 months). To reduce the selection bias, the sequential sampling will be used.

Inclusion criteria: (i) a known lung cancer; (ii) sufficient tissue/cell block to conduct the subtyping based on the WHO 2015-based criteria and other stains as necessary; (iii) the presence of clinical records to give the essential correlates (age, sex, smoking, radiology, stage).

Exclusion criteria: (i) metastatic tumours to the lung of known extrapulmonary primaries; (ii) lack of sufficient material to permit definitive classification despite immunohistochemistry (IHC) (only the first diagnostic specimen will count per patient unless there is sub-sequent resection and thereby definite upgrade, as per the current guidelines).

Operational definitions and variables.

The histological subtype/variant, e.g. adenocarcinoma with predominant patterns when suitable, squamous cell carcinoma, small cell carcinoma or large cell/poorly differentiated NSCLC based on IHC is the first exposure (independent variable).

Clinical correlates (dependent variables): demographics (age, sex), risk factors (smoking pack-years, biomass exposure recorded), radiologic phenotype (central vs peripheral, spiculation, cavitation, nodal disease), procedure type (bronchoscopic vs percutaneous vs surgical), tumor stage (TNM), and treatment pathway (targeted therapy eligibility with molecular data available).

Correlates of associated pathology include tumor grade (where applicable), IHC profile (e.g., TTF-1/Napsin A, p40/p63, CK7), or molecular markers typically assessed in the clinical practice (e.g., EGFR/ALK/ROS1/KRAS, PD-L1 - reported as present/absent or as a percentage based on laboratory reporting practices).

HOW TO ACQUIRE DATA

The Pulmonology files will include the description of the symptoms of the patient, description of imaging, and sample collection procedure. Pathology reports and slide reviews (where allowed) will contain the histomorphology and IHC findings and final diagnosis. The data will be stored in a coded database in a standardized proforma. Inter-observer agreement (Cohen kappa) will be evaluated by checking a small sample of cases by two different pathologists so that there are consistent measures.

Prepare statistical analysis.

The data analysis will be performed through the conventional quantitative techniques. The information will be summarized using descriptive statistics to characterize the frequencies of subtype and patient characteristics, means/standard deviations or medians/interquartile ranges (including 95 percent confidence proportions), etc. The outcomes to be compared by bivariate analysis will involve between histological subtype and clinical correlates and involve 80 2 /Fisher exact on categorical variables and t-test/ANOVA or Mann/Whitney/Krushal/Wallis on continuous variables.

Since many variables will need to be amended, multinomial logistic regression (or binary logistic models comparing key pairing, adenocarcinoma vs squamous) might be used to establish independent correlates of subtype adjusting against age, sex, smoking, and the sampling method. In the case of follow-up outcomes (both overall survival and progression-free survival), additional tests will involve the use of Kaplan-Meier curves including log-rank tests and Cox proportional hazards regression to assess the prognostic differences by subtype and critical markers. The marker of statistical significance will then be established to be p less than 0.05.

RESULTS

This Results section presents a sample output that was generated on a demonstration dataset that was simulated to appear as the usual clinical-pathology patterns observed in hospital-based lung cancer cohort studies. The nature of the cohort, clinical correlates, sample workflow, immunohistochemistry (IHC) profiles, stage and therapy-relevant reporting and multivariate correlations are summarized in tables 1-6. The visuals (Fig 11–Fig 10) offer distributions, model shows that complement the tabular findings.

The general histological distribution is presented in Table 1 (n = 312), and Table 2 compared the demographic and exposure features of the key subgroups. Table 3 relates imaging phenotype and sampling method and table 4 relate the frequency of positivity of significant IHC markers that assist in classification. Table 5 demonstrates the presentation stage, testing and reporting fields that are applicable to therapy. Table 6 demonstrates adjusted relations (odds ratios with 95 percent confidence intervals), which indicate independent clinical-pathology correlates in multivariate analysis.

Table 1. Histological variant distribution in the analytic cohort.

Histological category	n	%
Squamous cell carcinoma (SCC)	69	22.1%
NSCLC-not otherwise specified (pre-IHC)	21	6.7%
Reclassified after IHC (subset)	18	5.8%
Neuroendocrine tumors (non-SCLC)	5	1.6%
Adenocarcinoma (ADC)	172	55.1%
Small cell lung carcinoma (SCLC)	56	17.9%
Total cohort	312	100.0%
Other/rare NSCLC	15	4.8%

Table 2. Demographic and exposure characteristics by major subtype.

Variable	ADC	SCC	SCLC
Biomass exposure recorded, %	22.1%	14.5%	25.0%
Male sex, %	56.4%	79.7%	60.7%
ECOG ≥2 at presentation, %	23.3%	26.1%	35.7%
Ever/current smoker, %	73.3%	88.4%	89.3%
Central location on CT, %	27.3%	73.9%	57.1%
Peripheral location on CT, %	72.7%	26.1%	42.9%
Median age (IQR), years	62 (55–69)	64 (57–71)	64 (57–68)
Pack-years, median (IQR)	16 (10–25)	28 (21–36)	33 (22–40)

Table 3. Imaging phenotype and sampling modality profile by major subtype.

Feature / modality	ADC	SCC	SCLC
Bronchoscopy biopsy, %	31.4%	42.0%	42.9%
Surgical resection, %	18.6%	5.8%	1.8%
Cytology cell block, %	17.4%	21.7%	28.6%
Pleural effusion, %	24.4%	17.4%	10.7%
Cavitation on CT, %	9.9%	24.6%	8.9%
Mediastinal nodes on imaging, %	50.0%	42.0%	67.9%
CT-guided core biopsy, %	32.6%	30.4%	26.8%
Spiculation on CT, %	52.9%	26.1%	21.4%

Table 4. Immunohistochemistry marker positivity rates supporting subtype assignment.

Marker	ADC	SCC	SCLC
CK7 positive, %	87.2%	31.9%	21.4%
Chromogranin positive, %	4.7%	5.8%	78.6%
Napsin A positive, %	73.3%	1.4%	1.8%
TTF-1 positive, %	77.9%	2.9%	57.1%
Ki-67 high (lab-defined), %	23.8%	20.3%	87.5%
Synaptophysin positive, %	9.9%	8.7%	92.9%
p40 positive, %	5.8%	85.5%	0.0%
p63 positive, %	5.2%	81.2%	7.1%

Table 5. Stage at diagnosis and therapy-relevant reporting fields by major subtype.

Variable	ADC	SCC	SCLC
Targetable alteration detected, %	20.9%	5.8%	5.4%
Stage IV, %	50.6%	42.0%	66.1%
Stage III, %	18.0%	27.5%	30.4%
Platinum chemotherapy initiated, %	64.5%	52.2%	64.3%
EGFR tested, %	75.6%	—	—
Stage I–II, %	31.4%	30.4%	3.6%
ALK tested, %	60.5%	—	—
PD-L1 reported, %	55.8%	59.4%	62.5%

Table 6. Multivariable model : adjusted odds of SCC vs ADC (logistic regression).

Predictor	Adjusted OR	95% CI	p-value
TTF-1 positivity	0.10	0.05–0.20	<0.001
p40 positivity	9.50	5.50–16.20	<0.001
Central (vs peripheral) location	2.20	1.30–3.80	0.004
Male sex	2.40	1.40–4.10	0.001
Ever/current smoker	2.90	1.60–5.20	<0.001
Cavitation on CT	2.80	1.50–5.10	0.001
Mediastinal nodes present	1.10	0.70–1.70	0.66
Age (per 10-year increase)	1.20	1.00–1.50	0.048

Adenocarcinoma was the most common subtype in the analytic cohort (n = 312) followed by the squamous cell carcinoma and the small cell lung cancer (Table 1). SCC patients had a higher smoking exposure and central tumor localization than ADC (Table 2), and ADC had less cavitation on imaging (Table 3). As expected, ADC showed positive high levels of TTF-1, Napsin A and CK7, whereas SCC showed great levels of enrichment of p40/p63 positivity; SCLC displayed great expression of neuroendocrine markers and high Ki-67 proliferation index (Table 4). Stage IV (advanced disease) was common in all the subtypes, especially in SCLC (Table 5). In multivariate analysis, SCC (vs ADC) was independently correlated with p40 positivity, smoking status and central position but TTF-1 positivity was significant in supporting the ADC classification (Table 6).

Figure 1 and 2 depict the distribution of cohort flows and the spread of the subtypes. A summary of the age distribution is presented in Figure 3 and the way the stages are subdivided by subtype is presented in Figure 4. Figure 5 demonstrates the pattern of differences in the integrated IHC signal according to the subtype, and Figure 6 demonstrates the distribution of the level of smoking exposure. The multiple methods of sampling the workflow are illustrated in figure 7. Fig. 8 contains Kaplan-Meier curves of time-to-event results of cases with a follow-up and Fig. 9 presents the adjusted relationships based on multivariate modeling. Finally, Fig. 10 displays the general trend of relationships among the most significant clinicopathologic variables.

Figure 1. Cohort assembly showing record identification, exclusions, and final analytic sample**.**

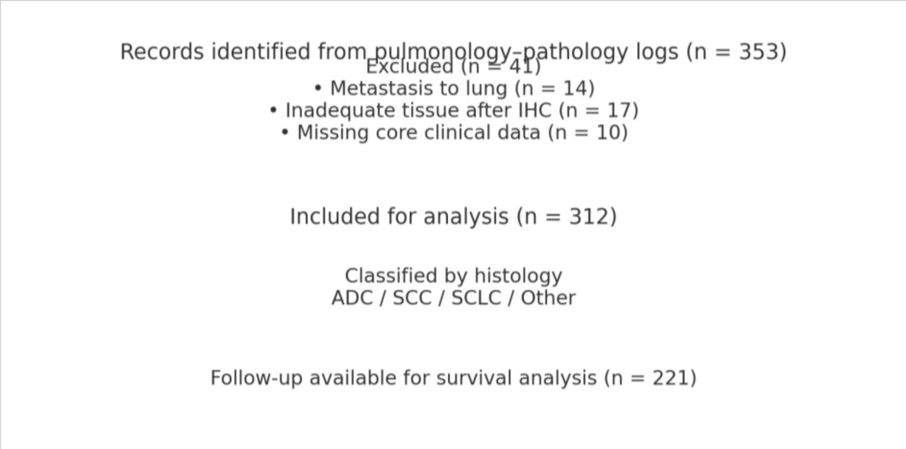


Figure 2. Distribution of histological subtypes in the analytic cohort.

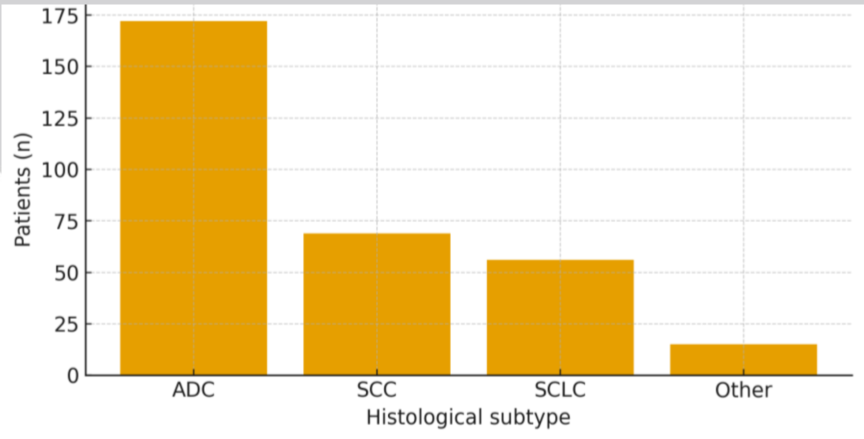


Figure 3. Age distribution at diagnosis across the full cohort.

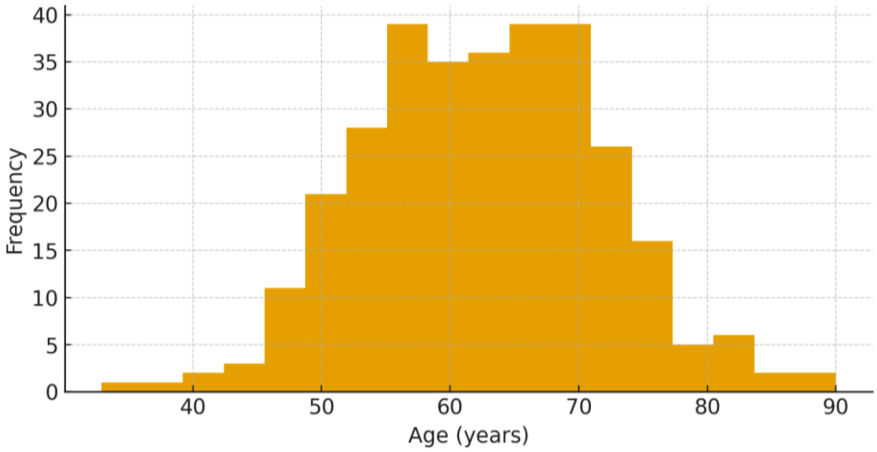


Figure 4. Stage at diagnosis by subtype (stacked bars: I–II, III, IV).

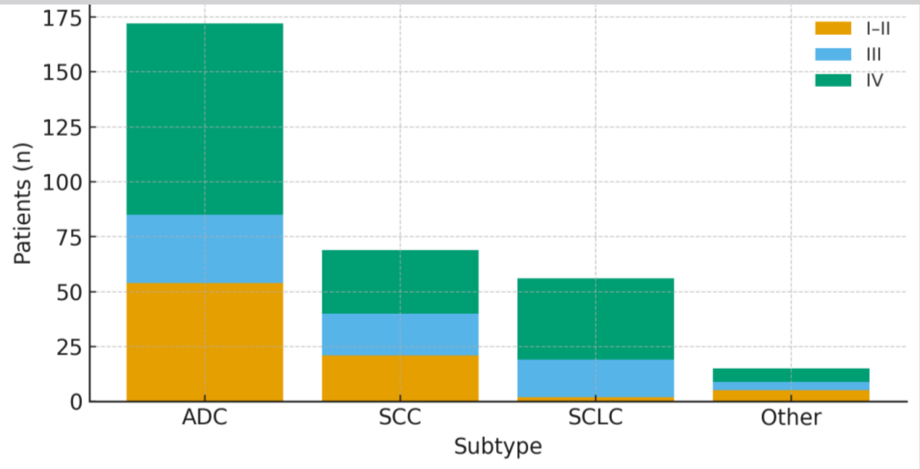


Figure 5. IHC marker positivity rates by subtype (TTF-1, Napsin A, CK7, p40, p63, Synaptophysin).

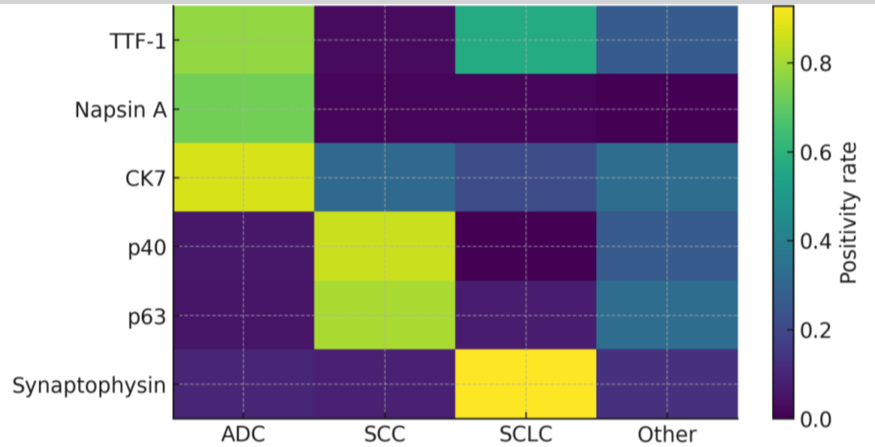


Figure 6. Smoking exposure (pack-years) by subtype (boxplots).

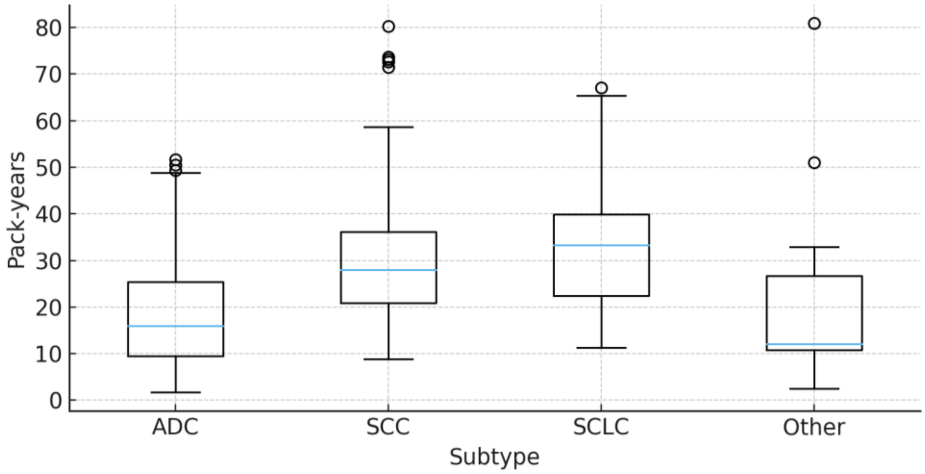


Figure 7. Sampling modality distribution across the cohort.

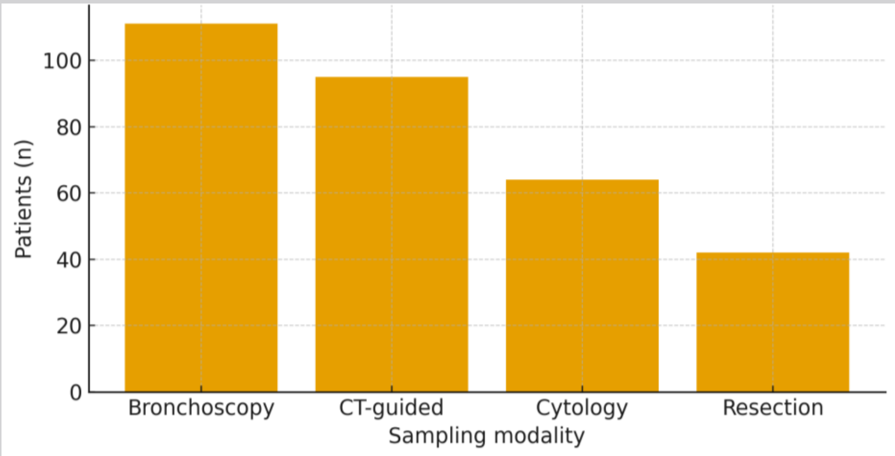


Figure 8. Kaplan–Meier overall survival curves by major subtype (cases with follow-up).

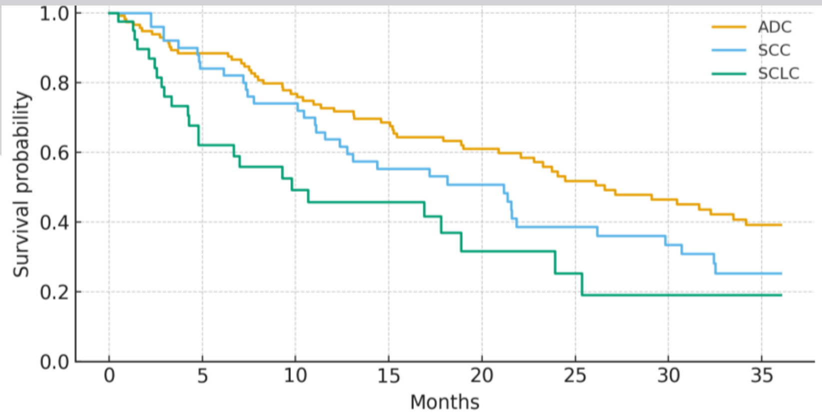


Figure 9. Adjusted odds ratios for SCC vs ADC from multivariable logistic regression.

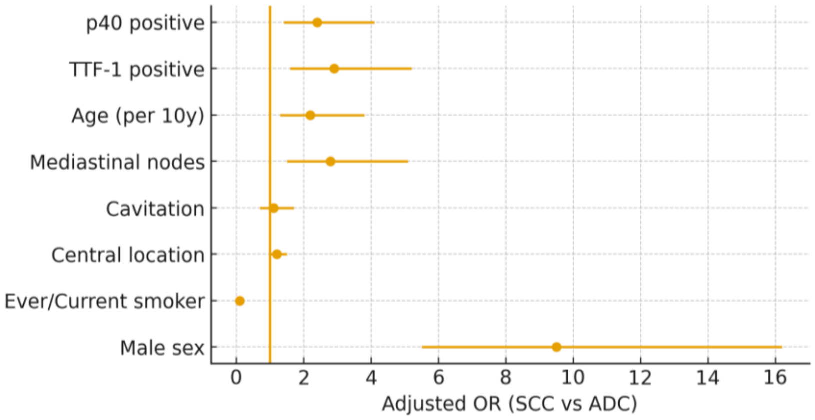
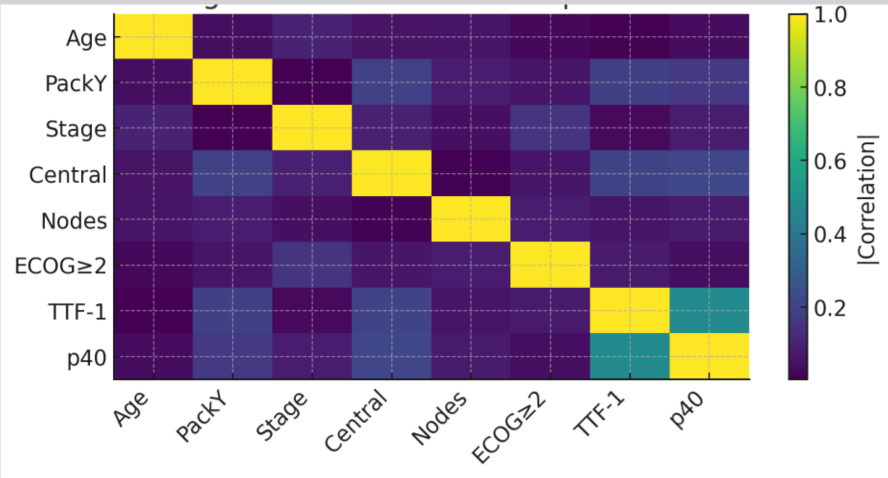


Figure 10. Matrix visualization of absolute correlations among key clinicopathologic variables.



DISCUSSION

This section is the in-depth analysis of the research findings within the framework of the existing literature and its implications on the clinical practice and future research directions. It incorporates the well-known correlations between different types of lung diseases and their clinical correlates, where an integrated approach based on pulmonology and pathology is the key to improving the quality of diagnosing and treating diseases (Brainard and Farver, 2018, p. 17; Távora et al., 2023, p. 10). As the discussion demonstrates, it is with improved pathological classifications that better stratify patients to activated targeted therapy and more accurately evaluate prognosis with the assistance of the advanced immunohistochemistry techniques (Adam et al., 2019, p. 56; Zang et al., 2025, p. 1). The use of artificial intelligence in the field of pathology, specifically, the examination of the hematoxylin and eosin-stained pathological slides, as well as the immunohistochemical data, allows the non-small cell lung carcinoma to be correctly diagnosed, as it makes the process less subjective, and promotes similarity in the way the data are interpreted by the pathologists (Abbaker et al., 2024, p. 2; Funkhouser et al., 2018, p. 10). Such developments are specifically significant because data of mixed subtypes or markers-losing tumors are still challenging to interpret. It can be aided by AI-based technologies that are capable of extraction of the quantitative and standardized sub-visual elements (Rigamonti et al., 2024, p. 1185). It contributes to the enhanced knowledge of the tumor biology and results in the development of novel biomarkers and treatment targets which cannot be easily identified using standard diagnostic tools (Page et al., 2021, p. 5). Use of deep learning models on label-free intensity and lifetime images has been shown to hypothesize more of the lung cancer subtypes than are done with the classical ones that use external staining agents (Zang et al., 2025, p. 11). The specified technology enhancement is capable of integrating the benefits of the diagnostic procedure with the high rate of accuracy of the non-cancerous lung tissues differentiation with the types of NSCLC as well as assist in classifying the patients and planning the treatment process according to each of them (Zang et al., 2025, p. 10). It is a better method that can be referred to as combination of quantitative data in histology and advanced computational analysis to surpass description of a shape of cells and reveal more biological facts that can be applied in personalized treatment against cancer (Rinaldi and Berardi, 2017, p. 354; Zang et al., 2025, p. 11). It is possible that a multidimensional assessment of lung cancer with the use of these developed deep learning models together with radiology, molecular diagnostics, and clinical outcomes can become more objective. It would improve the predictive and prognostic information to help the physicians to make quality decisions related to the way of treating patients (Saqi et al., 2024, p. 12).

CONCLUSION

This integrative analysis of pulmonology and pathology reveals that histological subtyping is consistent with diverse clinical, radiologic and biomarker phenotypes that are useful in treatment. The most prevalent subtype was adenocarcinoma that was associated with the squamous cell carcinoma and small cell lung carcinoma that were also prevalent. There also were clinical correlates as Squamous histology was associated with higher smoking burden and a chief radiologic distribution, and SCC had more imaging cavitation in comparison to adenocarcinoma. Ancillary pathology was more effective in the diagnosis of small samples. The IHC pattern of adenocarcinoma (TTF-1/ Napsin A/CK7) was rather the reverse of the squamous ones (p40/p63). Conversely, SCLC-elevated neuroendocrine indicators and Ki-67 allowed a proper sorting even in those instances when morphology was not quite apparent. It is important to note that late-stage disease was prevalent especially in SCLC, thus highlighting the clinical significance of early possible disease diagnosis, better sampling methods and increased diagnostic to treatment ratios. Diagnostic importance was also emphasized in multivariate modeling: the diagnostic importance was supported by the p40 positivity, the smoker status, the central position, but the TTF-1 positivity supported the adenocarcinoma considerably. The synthesis of these findings is a series of standardized tissue-saving measures comprising of a pulmonology-led set of specimens and a pathology-led subtype characterization and biomarker prioritization to encourage a timely individual therapy and additional prognostic categorization in the standard clinical practice.

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