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Correlation between epidermal growth factor receptor, anaplastic lymphoma kinase and programmed cell death-ligand-1 expression and survival in patients with pulmonary adenocarcinoma

Correlación entre la expresión y supervivencia del receptor del factor de crecimiento epidermal, la quinasa del linfoma anaplásico y el ligando-1 de la muerte celular programada en pacientes con adenocarcinoma pulmonar

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SUMMARY

Lung cancer is the leading cause of cancer incidence and mortality worldwide, accounting for 12.4 % of all reported cases. This study aims to investigate the relationship between patient survival and the expression of the markers EGFR, ALK, and PD-L1 in patients with lung adenocarcinoma. **Methods:** *A prospective cohort study was conducted at a cancer treatment center in Barranquilla, Colombia, involving patients aged 18 and older diagnosed with adenocarcinoma. Patient data, including demographics, tumor markers (EGFR, ALK, PD-L1), smoking history, and clinical outcomes, were collected. Statistical analyses included the Kolmogorov-Smirnov test, Kruskal-Wallis' test, Fisher's exact test, and Kaplan-Meier survival analysis.* **Results:** *The study included 193 patients, predominantly female (53 %), with a median age of 68 years. Most patients were from urban areas (86 %) and were smokers (48 %). The study found a high prevalence of poorly differentiated adenocarcinoma (54 %) and stage IV disease (86 %). Systemic metastasis was common (60 %), with a high mortality rate (79 %). Patients with PD-L1 expression % had a higher ECOG score, indicating worse functional status. The median overall survival was 23 months for EGFR-*

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mutant patients, significantly longer than for patients with other markers. High ECOG scores correlated with higher PD-L1 expression and worse outcomes. **Conclusion:** *Adenocarcinoma patients often present with advanced-stage disease, highlighting the need for early detection. PD-L1 expression and ECOG score are critical predictors of survival. Personalized therapy based on genetic markers such as EGFR, ALK, and PD-L1 can improve outcomes.*

Keywords: *Lung cancer, adenocarcinoma, EGFR, ALK, PD-L1, survival, biomarkers.*

RESUMEN

El cáncer de pulmón es la principal causa de incidencia y mortalidad por cáncer en todo el mundo y representa el 12,4 % de todos los casos notificados. Este estudio tiene como objetivo determinar la relación entre la supervivencia de pacientes con adenocarcinoma de pulmón y la expresión de los marcadores EGFR, ALK y PD-L1. **Métodos:** *Se realizó un estudio de cohorte prospectivo en un centro de tratamiento del cáncer en Barranquilla, Colombia, con pacientes de 18 años o más diagnosticados con adenocarcinoma. Se recopilaron datos de los pacientes, incluidos datos demográficos, marcadores tumorales (EGFR, ALK, PD-L1), antecedentes de tabaquismo y resultados clínicos. Los análisis estadísticos incluyeron la prueba de Kolmogórov-Smirnov, la prueba de Kruskal-Wallis, la prueba exacta de Fisher y el análisis de supervivencia de Kaplan-Meier.* **Resultados:** *Se incluyeron 193 pacientes, predominantemente mujeres (53 %), con una mediana de edad de 68 años. La mayoría de los pacientes procedían de zonas urbanas (86 %) y eran fumadores (48 %). El estudio encontró una alta prevalencia de adenocarcinoma poco diferenciado (54 %) y enfermedad en estadio IV (86 %). Las metástasis sistémicas fueron comunes (60 %), con una alta tasa de mortalidad (79 %). Los pacientes con expresión de PD-L1 ≥1 % tuvieron una puntuación ECOG más alta, lo que indica un peor estado funcional. La mediana de supervivencia general fue de 23 meses para los pacientes con mutación EGFR, significativamente más larga que para otros marcadores. Las puntuaciones altas del ECOG se correlacionaron con una mayor expresión de PD-L1 y peores resultados.* **Conclusión:** *Los pacientes con adenocarcinoma a menudo se presentan con enfermedad en estadio avanzado, lo que destaca la necesidad de una detección temprana. La expresión de PD-L1 y la puntuación ECOG son predictores críticos de supervivencia. La terapia personalizada basada en marcadores genéticos como EGFR, ALK y PD-L1 puede mejorar los resultados.*

Palabras clave: *Cáncer de pulmón, adenocarcinoma, EGFR, ALK, PD-L1, supervivencia, biomarcadores.*

INTRODUCTION

Lung cancer is the leading cause of cancer incidence and mortality worldwide, accounting for 12.4 % of all reported cases. It results from the combined action of multiple factors that damage the bronchial epithelium, making it the leading cause of mortality in the Western world. The primary environmental agent involved in lung carcinogenesis is tobacco; however, there is also an association between occupational exposure to substances such as biomass, asbestos, and radon, and the occurrence of lung cancer (1,2).

During the development of non-small cell lung cancer (NSCLC), various molecular events occur, including loss of heterozygosity, epigenetic changes, and mutations in genes such as p53, K-RAS, and the epidermal growth factor receptor (EGFR) (1,3). EGFR, located on the short arm of chromosome 7, is part of the tyrosine kinase receptor (TK) family, known as the HER or ErbB family. This family includes four members that regulate metabolic and histological processes: EGFR (HER1/ErbB1), HER2 (ErbB2), HER3 (ErbB3), and ErbB4 (4,5).

For patients diagnosed with adenocarcinoma, it is recommended to test for the expression of Anaplastic Lymphoma Kinase (ALK), programmed cell death-ligand 1 (PD-L1), and EGFR, which are present in approximately 30 % of patients (6,7). Targeted therapy based on these markers has shown a positive impact on survival, especially in patients with overexpression of PD-L1 (>50 %), who present a survival rate of over 25 % at five years (8).

The markers EGFR, ALK, and PD-L1 play a crucial role in patient survival (9). Global studies have found worse initial survival rates in those with PD-L1 expression levels greater than 1 %. Studies in Latin America, where the prevalence of EGFR mutations and difficulties in obtaining immunohistochemistry results lead to late diagnoses, highlight the need to detect these mutations and overexpression early. This study aims to investigate the relationship between

patient survival and the expression of EGFR, ALK, and PD-L1 markers in patients with lung adenocarcinoma.

MATERIALS AND METHODS

1. Study Design: Patients and Variables

A prospective, analytical observational cohort study was conducted at a referral center in Barranquilla (Atl, CO) for the management of oncology patients. Patients over 18 years old were selected who had undergone a histopathological diagnosis at the center where treatment was carried out or had been referred after diagnosis, with their treatment entirely conducted at the center where the data were collected.

The medical records of the patients were reviewed. A database was created with the following variables: Sex (Female/Male), Age (in completed years), Place of Residence (rural or urban), Economic Occupation, Date of Diagnosis, Immunohistochemical Description, Histopathological Staging, Expression of EGFR/ALK/PDL1 markers, Tumor Proportion Score (TPS), Smoking History (Never Smoker, Smoker), Vital Status (Deceased/Alive), Date of Death, Exposure to Biomass Combustion (EBC), Eastern Cooperative Oncology Group (ECOG) score, Pharmacological Therapy (Platinum-Based Antineoplastic (PBA); Mitotic Inhibitors (MI); Tyrosine Kinase Inhibitors (TKI); Anti-Programmed Death-1 (Anti_PD-1), and Type of Metastasis (Local, Regional, Systemic).

2. Statistical Analysis

Data normality was analyzed using the Kolmogorov-Smirnov test. Quantitative variables were presented as medians and interquartile ranges. Absolute and relative frequencies were used to describe categorical variables. Kruskal-Wallis' test was used to evaluate the medians obtained by patients according to the TPS stratification group of PD-L1 (<1 %, 1-49 %, ≥50 %). Fisher's exact test was used to analyze categorical variables. The relationship between the score and molecular markers (EGFR, PD-L1, and ALK) was explored through simple correspondence analysis. Kaplan-Meier analysis was conducted to estimate overall survival between groups. To identify possible clinicopathological factors associated with mortality, multivariate logistic regression analysis was performed, adjusting for the variables using the backward methodology. Odds ratios (ORs) and 95 % confidence intervals (CIs) were reported for each variable. A p-value <0.05 was considered statistically significant. R-CRAN software version 4.3.2 was used for statistical analysis.

RESULTS

1. General Characteristics

A total of 193 patients diagnosed with pulmonary adenocarcinoma were included. Most patients were female (53 %), with a median age of 68 years (interquartile range, IQR: 38-89 years). Seventy-five percent of the patients were over 61 years old. Eighty-six percent of the patients were from urban areas. Approximately half of the patients were smokers (48 %), and 37 % were homemakers. Of the total number of patients, 35 cases (18 %) were exposed to biomass combustion (Table 1).

Table 1. Characteristics of patients with lung adenocarcinoma

Characteristic	n = 193[1]
Age	68 (38-89)
Sex	
Female	103 (53 %)
Male	90 (47 %)
Area	
Rural	27 (14 %)
Urban	166 (86 %)
Work status	
Employee	36 (19 %)
Homemaker	71 (37 %)
Pensioner	35 (18 %)
Unemployed	45 (23 %)
Smoking history	
Never-smoker	100 (52 %)
Smoker	93 (48 %)
EBC	35 (18 %)

EBC, exposure to biomass combustion; [1]Median (Range); n (%)

No significant differences were observed when comparing the age between males (Median: 68, IQR: 43-87) and females (Median: 69, IQR: 38-89 years) (p=0.68).

2. Clinicopathological Characteristics and Outcomes

Many patients had poorly differentiated adenocarcinoma (54 %). The most common tumor stage was stage IV (86 %), followed by stage IA (3.6 %) and stage IIA (3.6 %). Systemic metastasis (60 %) was the most frequent clinical presentation. Most patients received platinum-based antineoplastics (PBA) (62 %), followed by mitotic inhibitors (MI) (45 %). Eleven cases (6 %) received biological therapy. The most common Tumor Proportion Score (TPS) for PD-L1 was <1 % (39 %). Regarding driver oncogenes, 26 cases (76 %) had an EGFR mutation, and 8 cases (24 %) had EML4-ALK rearrangements. A total of 153 patients (79 %) died (Table 2).

Table 2. Clinical and Pathologic Characteristics of Patients with Lung Adenocarcinoma

Characteristic	(n=193) [1]
ECOG Score	2 (0 - 4)
Adenocarcinoma	
Well Differentiated	6 (5.1 %)
Moderately Differentiated	48 (41 %)
Poorly Differentiated	64 (54 %)
Stage	
IA	7 (3.6 %)
IB	1 (0.5 %)
IIA	7 (3.6 %)
IIIA	6 (3.1 %)
IIIB	6 (3.1 %)
IV	166 (86 %)
Metastasis type	
Local	49 (29 %)
Regional	19 (11 %)
Systemic	100 (60 %)
Drug Therapy	
PBA	119 (62 %)
MI	87 (45 %)
TKI	25 (13 %)
Anti_PD-1	11 (6 %)
PD-L1 TPS	
<1	12 (39 %)
1-49	11 (35 %)
≥50%	8 (26 %)
Oncogenic Driver	
EGFR	26 (76 %)
EML4-ALK	8 (24 %)
Death	153 (79 %)

TPS, tumor proportion score; EBC, exposure to biomass combustion; ECOG, Eastern Cooperative Oncology Group; PBA, Platinum-based antineoplastic; MI, Mitotic inhibitors; TKI, tyrosine kinase inhibitors; PD-1, programmed cell death protein 1; [1]Median (Range); n (%)

3. ECOG Score, Molecular Markers, and Outcome

A simple correspondence analysis was performed to explore the relationship between the Eastern Cooperative Oncology Group (ECOG) score and the genetic markers PD-L1, EGFR, and EML4-ALK. The ECOG score was stratified as mild (0-1), moderate (2-3), and severe (4). An important association was observed between patients with a moderate ECOG score and PD-L1 TPS ≥1 % (Figure 1).

With respect to outcomes, it was observed that deceased patients had a significantly higher ECOG score compared to survivors (Median: 2, IQR: 0-4 vs. Median: 1, IQR: 0-4, p=<0.0001) (Figure 2).

4. Cell Differentiation Grade and Overall Survival

In this study, lung adenocarcinomas were classified as follows: Well-differentiated (score 2): Solid pattern < 90 % and mild/moderate atypia. Moderately differentiated (score 3): Solid pattern ≥ 90 % and mild/moderate atypia; or solid pattern < 90 % and severe atypia. Poorly differentiated (score 4): Solid pattern ≥ 90 % and severe atypia. Of the total patients, 64 (54 %) had poorly differentiated lung adenocarcinoma, 45 (41 %) had moderately differentiated adenocarcinoma, and 6 (5.1 %) had well-differentiated adenocarcinoma. The influence of cell differentiation grade on overall survival was explored (Figure 3).

The median overall survival was 10.8 months for patients with well-differentiated adenocarcinoma, 8.7 months for moderately

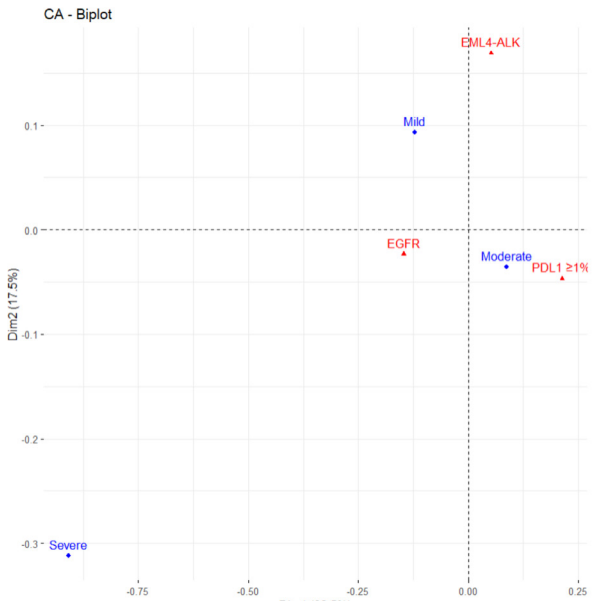

Figure 1. Simple correspondence analysis between ECOG score and molecular markers PD-L1, EGFR, and EML4-ALK.

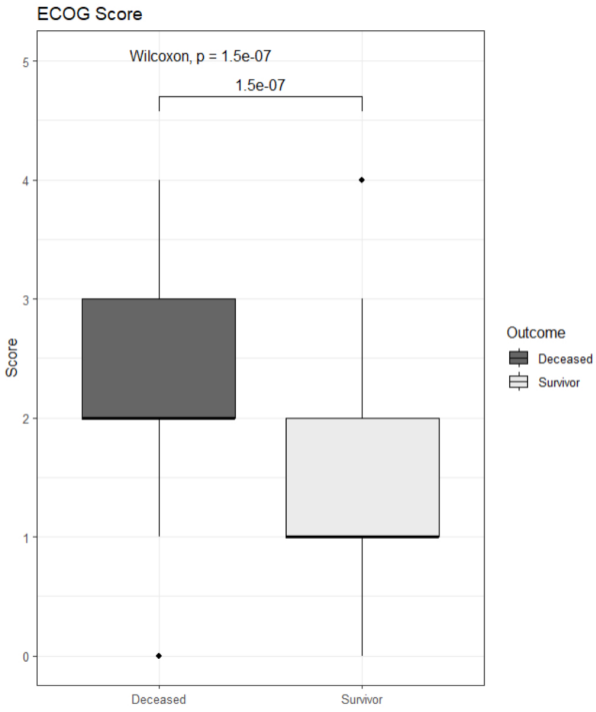

Figure 2. ECOG Score by Outcome (Deceased vs. Survivors).

differentiated adenocarcinoma, and 5 months for poorly differentiated adenocarcinoma. However, no significant differences were observed between the groups (p=0.41) (Figure 3).

5. PD-L1 TPS in Lung Adenocarcinoma

Of the 193 lung adenocarcinoma specimens analyzed, 19 cases (10.1 %) had a PD-L1 Tumor Proportion Score (TPS) of ≥1 %. The PD-L1 TPS for patients with EGFR mutations or ALK rearrangements is presented in Table 3. Patients with a PD-L1 TPS of ≥1 % were further divided into groups with a PD-L1 TPS of 1 % to 49 % (n=11, 6 %) or ≥50 % (n=8, 3 %). However, no significant associations were observed between the clinicopathological characteristics and/or outcomes of the patients and the PD-L1 TPS stratified as <1 %, 1 %-49 %, or ≥50 % (p>0.05) (Table 3).

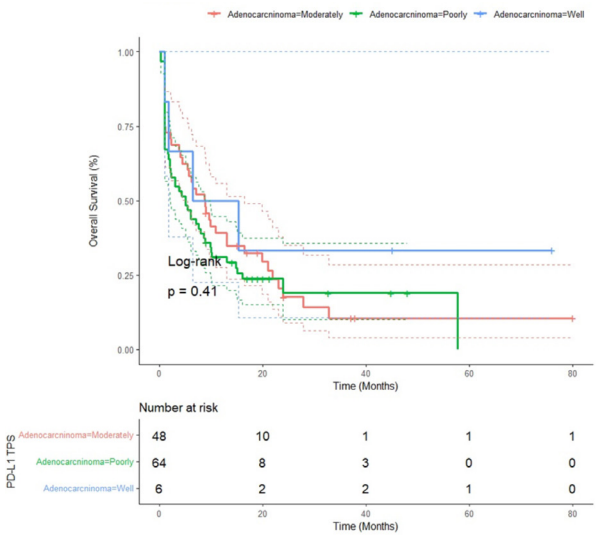

Figure 3. Kaplan-Meier Survival Curve for Overall Survival in Patients with Lung Adenocarcinoma by Cell Differentiation Grade.

Table 3. Association analysis for PD-L1 expression (TPS of<1 %, 1 % to 49 %, or ≥50 %) and clinical features.

Characteristic	PD-L1 expression levels			p-value
	TPS <1 % (n=12) [1]	TPS 1-49 % (n=11) [1]	TPS ≥50 % (n=8) [1]	
Age	73 (38, 83)	74 (55, 84)	65 (47, 78)	0.5[2]
Sex				0.7[3]
Female	4 (33 %)	5 (45 %)	2 (25 %)	
Male	8 (67 %)	6 (55 %)	6 (75 %)	
Smoking history				0.2[3]
Never-smoker	8 (67 %)	5 (45 %)	2 (25 %)	
Smoker	4 (33 %)	6 (55 %)	6 (75 %)	
EBC	1 (8.3 %)	0 (0 %)	0 (0 %)	>0.9[3]
ECOG score	2 (1, 3)	2 (1, 3)	2 (0, 3)	0.9[2]
Stage				0.13[3]
IIA	0 (0 %)	2 (18 %)	0 (0 %)	
IV	12 (100 %)	8 (73 %)	8 (100 %)	
Metastasis type				0.2[3]
Local	3 (25 %)	0 (0 %)	2 (29 %)	
Regional	2 (17 %)	0 (0 %)	2 (29 %)	
Systemic	7 (58 %)	8 (100 %)	3 (43 %)	
Drug Therapy				
PBA	6 (50 %)	6 (55 %)	5 (63 %)	>0.9[3]
MI	5 (42 %)	3 (27 %)	3 (38 %)	0.9[3]
TKI	5 (42 %)	2 (18 %)	1 (13 %)	0.4[3]
Anti_PD-1	1 (8.3 %)	1 (9.1 %)	4 (50 %)	0.086[3]
Oncogenic Driver				>0.9[3]
EGFR	5 (63 %)	2 (100 %)	1 (100 %)	
EML4-ALK	3 (38 %)	0 (0 %)	0 (0 %)	
Death	7 (64 %)	11 (92 %)	7 (88 %)	0.2[3]

TPS: Tumor Proportion Score; EBC: Exposure to Biomass Combustion; ECOG: Eastern Cooperative Oncology Group; PBA: Platinum-based Antineoplastic; MI: Mitotic inhibitors; TKI: Tyrosine kinase inhibitors; PD-1: Programmed cell death protein 1; [1] Median (Range); n (%); [2] Kruskal-Walli's rank sum test; [3] Fisher's exact test.

6. Molecular Markers and Overall Survival

When evaluating the overall survival of patients with lung adenocarcinoma based on the molecular marker present, significant differences were observed in the median overall survival in months according to the marker. The median survival for patients with EGFR mutations was 23 months, for those with EML4-ALK rearrangements, it was 16 months, and according to PD-L1 TPS, it was 9 months for patients with TPS <1 % and 5.5 months for those with TPS ≥1 % ($p = 0.036$) (Figure 4).

7. PD-L1 TPS and Overall Survival

To assess how PD-L1 expression might influence the survival of patients with lung adenocarcinoma, overall survival was analyzed based on the PD-L1 TPS. The median survival for patients with a PD-L1 TPS <1 % was 14 months, for those with a PD-L1 TPS of 1-49 % it was 8.5 months, and for cases with a PD-L1 TPS >50 % it was 5.5 months. Comparing the three groups of patients stratified by PD-L1 tumor proportion score (TPS), a trend toward decreased overall survival was observed as PD-L1 TPS increased. However, no significant differences were found based on PD-L1 TPS (Figure 5).

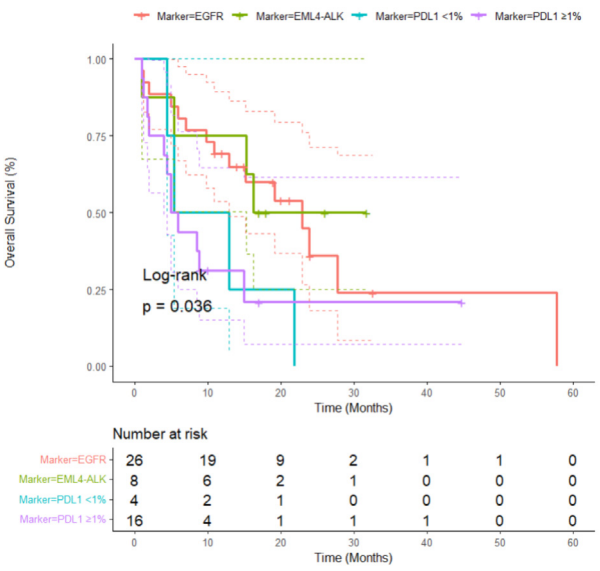

Figure 4. Kaplan-Meier Survival Curve for Overall Survival in Patients with Lung Adenocarcinoma by Molecular Marker.

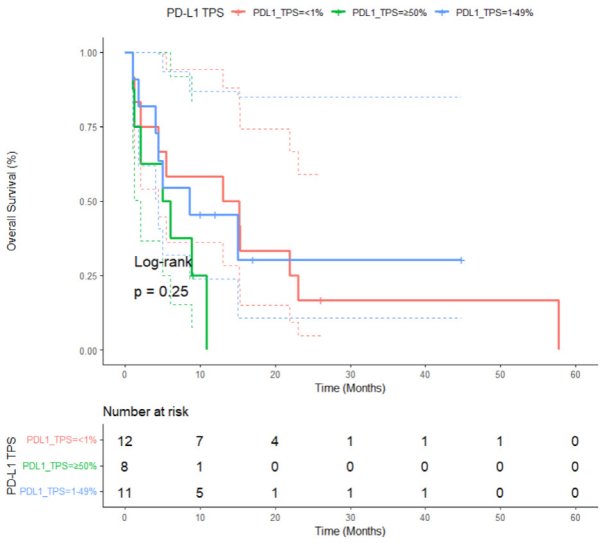

Figure 5. Kaplan-Meier Survival Curve for Overall Survival in Patients with Lung Adenocarcinoma by PD-L1 TPS Stratification.

8. Factors Associated with Mortality

As shown in Table 4, a multivariate logistic regression analysis was performed to identify possible clinicopathological factors associated with mortality in patients with lung adenocarcinoma. It was found that male sex and an ECOG score of 2-3 were associated with a higher risk of mortality. In the adjusted model, male patients were 4.5 times more likely to die compared to female patients (OR: 4.5, 95 % CI: 1.6-18.1, p=0.04). Patients with an ECOG score of 2-3 were 7.3 times more likely to die compared to those with an ECOG score of 4 (OR: 7.3, 95 % CI: 1.89-28.9, p=0.003).

DISCUSSION

Sex (53 % women), age (75 % >61 years), urban residency (86 %), high smoking rate (48 %), and exposure to biomass combustion (EBC) (18 %) are contributing factors to the development of pulmonary adenocarcinoma. In urban areas, there is greater exposure to fine particulate matter (PM2.5 and PM10) and other volatile compounds (10,11). Adenocarcinomas in patients from urban areas often exhibit mixed patterns, including lepidic, acinar, and papillary components. This diversity could be a result of exposure to multiple carcinogens, inducing various pathways of cellular transformation (12).

Smoking is the most studied risk factor and is correlated with specific mutations in genes such as KRAS and TP53. More recently, it has also been associated with alterations in EGFR in lung adenocarcinomas. These mutations are more prevalent in smokers and contribute to carcinogenesis by activating oncogenic pathways and inhibiting DNA repair mechanisms. Adenocarcinomas in smokers tend to exhibit poorer differentiation and a more aggressive phenotype, with a higher degree of vascular and pleural invasion (10,13,14). Additionally, exposure to biomass combustion is a significant risk factor, especially among women in rural or semi-urban areas. This exposure is associated with the inhalation of a complex mixture of organic and inorganic compounds that can induce chronic interstitial inflammation and

Table 4. Multivariate Analysis of Overall Survival in Relation to Clinicopathologic Characteristics

Characteristic	Multivariate			Adjusted		
	OR[1]	95 % CI[2]	p-value	OR[1]	95 % CI[2]	p-value
Age >55 years	0.39	0.03, 5.26	0.5	0.45	0.07, 2.90	0.4
Sex						
Female	—	—		—	—	
Male	11.0	0.87, 139	0.053	4.52	1.6, 18.1	0.041
Smoking history						
Smoker	1.02	0.11, 9.14	>0.9	0.90	0.19, 4.14	0.9
EBC						
Yes	0.49	0.02, 12.1	0.7			
ECOG						
2-3	4.43	0.48, 41.2	0.2	7.39	1.89, 28.9	0.003
4	3.05	0.09, 106	0.5	2.52	0.08, 80.1	0.6
Grading						
Poorly Differentiated	0.25	0.03, 2.41	0.2			
Well Differentiated	1.64	0.03, 79.9	0.8			
Stage						
III	—	—				
IV	0.95	0.01, 125	>0.9			
Metastasis type						
Regional	0.32	0.01, 8.84	0.5	0.67	0.10, 4.41	0.7
Systemic	2.44	0.26, 22.6	0.4	2.55	0.66, 9.85	0.2
PD-L1 TPS						
<1 %	—	—				
≥50 %	0.54	0.03, 9.01	0.6			
1-49 %	0.34	0.02, 6.90	0.5			
EGFR Mutation						
Yes	0.68	0.05, 9.35	0.8			
ALK rearrangements						
Yes	0.85	0.03, 22.2	>0.9	0.23	0.04, 1.50	0.12
PBA						
Yes	1.19	0.07, 19.9	>0.9			
MI						
Yes	4.93	0.27, 90.0	0.3			
TKI						
Yes	0.26	0.02, 4.23	0.3			

[1]OR = Odds Ratio, [2]CI = Confidence Interval.

fibrosis, as well as oxidative stress, along with a predominantly acinar histological pattern (15).

The predominance of poorly differentiated adenocarcinoma (54 %) and stage IV (86 %) indicates late diagnosis and significant cancer aggressiveness in the studied sample. The high frequency of systemic metastasis (60 %) and the elevated mortality rate (79 %) underscore the lethality of the disease and the critical importance of early detection and treatment (16,17). The choice of platinum-based antineoplastics in most cases (62 %) reflects standard clinical practice, while the use of biological therapy in only 6 % of cases suggests limitations in access or patient selection based on biomarkers (18,19).

The significant association between a moderate ECOG score (2-3) and PD-L1 TPS ≥1 % highlights the correlation between functional impairment and PD-L1 expression. This suggests that inflammation and immune dysfunction may

play a role in disease progression. Additionally, the fact that deceased patients had a significantly higher ECOG score indicates a clear relationship between functional quality at diagnosis and survival. This relationship highlights the interaction between patient functional capacity and the tumor microenvironment, particularly regarding inflammation and immunity (20,21).

PD-L1 is a protein that normally helps regulate the immune response to avoid autoimmunity. However, in the context of cancer, many tumor cells express PD-L1 to evade the host immune response. PD-L1 expression on tumor cells and in the immune stroma can inhibit the cytotoxic activity of T cells, allowing the tumor to progress. High PD-L1 expression is associated with dense infiltration of immune cells, particularly regulatory T cells (Tregs) and tumor-associated macrophages (TAMs), which promote immunosuppression and facilitate tumor immune evasion (20,21).

Lung adenocarcinomas with higher PD-L1 expression may exhibit a more disorganized growth pattern, indicating tumor aggressiveness and interaction with the microenvironment to facilitate tumor cell survival and proliferation. The correlation between an ECOG score of 2-3 and higher PD-L1 expression (TPS ≥1 %) suggests that functional impairment may be both a consequence and a facilitator of cancer progression (22).

Systemic inflammation, often reflected by markers such as C-reactive protein (CRP) and interleukin-6 (IL-6), can promote the expression of PD-L1 in tumor cells. Patients with compromised functional status may have upregulated PD-L1 as a reflection of generalized immune dysfunction, which includes the activation of pathways promoting immunosuppression and facilitating tumor progression (23,24).

High PD-L1 expression and increased ECOG score are predictors of poorer prognosis in patients with lung adenocarcinoma. High PD-L1 expression can confer resistance to conventional therapies such as chemotherapy and radiotherapy, as these tumor cells are protected from treatment-induced apoptosis. Acting as an immunosuppressive facilitator, it allows tumor cells to evade immune surveillance, increasing the risk of metastasis and contributing to a more deteriorated functional state (20,21).

Survival analysis revealed significant differences based on molecular markers, with a median survival of 23 months for patients with EGFR mutation, significantly longer than for those with other markers. These results are consistent with the literature, which suggests that EGFR mutations are associated with a better response to targeted therapies. In contrast, the low survival in patients with PD-L1 TPS <1 % and ≥1 % highlights the complexity of this biomarker as a predictor of treatment response, particularly to immune checkpoint inhibitors (18,19).

The multivariate analysis identified male sex and an ECOG score of 2-3 as significant factors associated with higher mortality. This reflects previous findings where men and patients with greater functional impairment have worse outcomes. These factors should be considered in risk stratification and treatment personalization (25,26).

CONCLUSIONS

The high prevalence of poorly differentiated adenocarcinoma (54 %) and the majority of patients presenting at stage IV (86 %) indicate a failure in early detection strategies. Furthermore, the clear correlation between PD-L1 expression and the worsening functional status of patients (ECOG) suggests that inflammation and immune dysfunction play significant roles in lung cancer progression. Therefore, immunotherapeutic strategies targeting PD-L1 could offer a promising therapeutic approach for these patients.

Moreover, the findings reinforce the importance of targeted therapies in improving outcomes for patients with specific mutations (EGFR). Personalized treatment based on the tumor's genetic profile could offer better clinical outcomes and should be considered standard practice. Integrating different strategies could significantly improve survival rates and quality of life for patients, especially those focusing on evaluating targeted therapies and immunotherapies for aggressive forms of lung cancer.

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Informed Consent Statement: Patient consent was waived due to REASON the study was based solely on the review of medical records and many of the patients had passed away. Therefore, the Ethics Committee granted authorization for the review of the database. This decision was made considering the impossibility of obtaining consent from deceased patients and the importance of the research in improving the understanding and treatment of lung adenocarcinoma.

Data Availability Statement: All data underlying the results are available as part of this article.

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