STK11 EXPRESSION AS A POTENTIAL PROGNOSTIC BIOMARKER IN LUNG CANCER

EXPRESSÃO DE STK11 COMO UM POTENCIAL BIOMARCADOR PROGNÓSTICO NO CÂNCER DE PULMÃO

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ABSTRACT

Lung cancer is a group of neoplastic diseases with the primary site being the lungs. For advanced lung adenocarcinoma, immunotherapy blocking PD-1/PD-L1 has become a key treatment, improving survival. However, response markers like PD-L1 expression remain imperfect. Notably, mutations in the tumor suppressor gene *STK11*, common in adenocarcinomas, are linked to immunosuppressive microenvironments and reduced immunotherapy efficacy. This study evaluated the relationship between *STK11* expression and the prognosis of lung cancer. We analyzed "The Cancer Genome Atlas" (TCGA) database from the National Institute of Health (NIH/USA), correlating clinical and pathological data. We found that *STK11* has the highest mutation frequency in lung adenocarcinoma (86.32%), primarily through substitution mutations (76.6%). The presence of this mutation is not associated with a worse prognosis. Therefore, it is concluded that further research is needed to fully understand the impact of *STK11* mutations and their potential as a therapeutic response marker, as well as their association with the development of new tumor suppressor therapies.

Keywords: *STK11*, lung cancer, biomarker, prognosis, LKB1.

RESUMO

O câncer de pulmão é um grupo de doenças neoplásicas cujo sítio primário são os pulmões. No adenocarcinoma pulmonar avançado, a imunoterapia com bloqueio de PD-1/PD-L1 tornou-se um tratamento fundamental, melhorando a sobrevida. No entanto, marcadores de resposta, como a expressão de PD-L1, ainda são imperfeitos. Notavelmente, mutações no gene supressor tumoral STK11, comuns em adenocarcinomas, estão associadas a microambientes imunossupressores e à

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redução da eficácia da imunoterapia. Este estudo avaliou a relação entre a expressão de STK11 e o prognóstico do câncer de pulmão. Foram analisados dados do banco The Cancer Genome Atlas (TCGA), do National Institutes of Health (NIH/EUA), correlacionando informações clínicas e anatomopatológicas.Foi observado que o STK11 apresenta a maior frequência de mutações no adenocarcinoma pulmonar (86,32%), principalmente por mutações de substituição (76,6%). A presença dessa mutação não foi associada a pior prognóstico. Conclui-se que são necessárias mais pesquisas para compreender plenamente o impacto das mutações em STK11 e seu potencial como marcador de resposta terapêutica, bem como sua associação com o desenvolvimento de novas terapias baseadas em genes supressores tumorais.

Palavras-chave: *STK11; câncer de pulmão; biomarcador; prognóstico; LKB1.*

1 INTRODUCTION

Lung cancer is a group of neoplastic diseases with the primary site being the lungs. However, in order to facilitate treatment guidelines, the World Health Organization classifies lung cancer into groups based on the cellular type and genetic alterations of the initial tumor cell lineage (Ettinger *et al.,* 2018). Typically, there is a first division into two major groups: small cell lung cancer and non-small cell lung cancer. Small cell lung cancer represents on average 14% of lung cancer cases and is characterized by its aggressiveness (Boloker; Wang; Zhang, 2018). On the other hand, non-small cell lung cancer accounts for approximately 84% of diagnoses and is a heterogeneous group that includes different histological types, such as squamous cell carcinoma, adenocarcinomas, large cell carcinoma, and other rarer types. Each of these types and subtypes represents a distinct disease with its own molecular characteristics and, consequently, requires a more specific treatment based on the stage of the disease and the patient's physical condition. Among all types of lung cancer, adenocarcinoma is the most frequent, and its incidence is increasing compared to other types (Ettinger *et al.,* 2018).

It is important to emphasize that metastatic lung adenocarcinoma treatment has recently achieved a significant milestone with the introduction of immunotherapy using monoclonal antibodies against programmed cell death protein 1 (PD-1) or programmed cell death ligand 1 (PD-L1) for tumors with high PD-L1 (Hanna *et al.,* 2017; Vokes *et al.,* 2018). PD-1 is a negative co-stimulatory receptor expressed on the surface of T lymphocytes. When it binds to its ligand, it inhibits the cytotoxic response of T cells, preventing the immune system from eliminating tumor cells that express PD-L1.

Therefore, the use of antibodies that block the binding of PD-1 to its ligand allows the patient's immune system to fight the tumor (Schreiber; Old; Smyth, 2011). Despite lung cancer still being the most common and deadliest cancer in the world, the introduction of these agents has significantly increased the survival of patients with advanced disease (Vokes *et al.,* 2018). However, this therapy is expensive, and there are still many controversies regarding the ideal therapeutic response marker. In addition to analyzing PD-L1 expression in different tissues, various other markers are commonly studied, analyzing their association or not with PD-L1 expression. These markers include tumor mutational burden, lymphocyte infiltration in the tumor, and others. There are several molecular alterations in adenocarcinomas that are already used in therapy, and others are being studied as prognostic predictors and therapy selection markers. However, none of them have a well-established correlation with the therapeutic response to PD-1 and PD-L1 immunotherapy (Duruisseaux *et al.*; Gandara *et al.,* 2018).

STK11 (serine/threonine kinase 11) is a tumor suppressor gene involved in cellular metabolism and growth and is mutated in 15-35% of lung adenocarcinomas (Imielinski *et al.,* 2012). In order to better understand mechanisms related to these alterations of this gene in lung adenocarcinoma, in recent years, *STK11* has been the focus of several studies, and its inactivation has been recently associated with inert tumor microenvironments, reducing the antitumor response to immunotherapeutic approaches in both mice and humans (Skoulidis *et al.,* 2018; Kadara *et al.,* 2017; Koyama *et al.,* 2016).

In this context, this study evaluated the relationship between *STK11* expression and the prognosis of lung cancer based on data from studies available in "The Cancer Genome Atlas" (TCGA) database of the National Institute of Health (NIH/USA). The TCGA database provides genetic profiles, DNA sequencing, and transcriptome data from hundreds of samples of various types of cancer.

2 MATERIAL AND METHODS

Data encompassing the genome, median survival, and patient characteristics (sex, ethnicity, number of mutations, mutation type and tumor histology) were obtained from The Cancer Genome Atlas (TCGA) of the National Institutes of Health (NIH/USA). The data were accessed through the GDC data portal (https://portal.gdc.cancer.gov/)

in March 2021. The relationship between *STK11* expression and clinical data was analyzed using spreadsheets in Microsoft Excel 2016.

Statistical analysis was performed using GraphPad Prism software (version 9.1.2 for Windows, GraphPad Software, LLC). Chi-square test was used to assess differences among patients. A p-value of <0.05 was considered statistically significant.

3 RESULTS

A total of 11,961 samples from lung cancer patients were found, out of which 242 samples had *STK11* gene data available in the TCGA database. Among these, 48.35% (n=117) exhibited a mutation profile in the *STK11*, but only 103 cases had the analysis of the type of mutation. Regarding the type of mutation (Table 1), a predominance of substitution cases was observed, accounting for 60.68% of the total analyzed.

Table 1 - Most common types of mutations in *STK11* in patients with lung cancer.

Mutation type	**Number of cases (n=117)**	**Percentage (%)**
Substitution	71	60.68
Deletion	21	17.95
Insertion	11	9.40
Not available	14	11.97

Source: The Authors (2025)

Adenocarcinomas were more associated to *STK11* mutations (Table 2, p<0.0001). STK11 mutations had no relation with ethnicity (Table 3). Although, there is no difference in *STK11* mutation due the sex (Table 4).

Table 2 - Most common histological types among patients with lung cancer and mutated *STK11*.

Histological type	**Without *STK11* mutation (n=125)**	**With *STK11* mutation (n=117)**	**P-value**
Adenomas and adenocarcinomas	46	101	<0.0001
Other tumor types	79	16	

Source: The Authors (2025)

Table 3 - Distribution of patients with lung cancer and mutated *STK11* by ethnicity.

Ethnicity	**Without *STK11* mutation (n=125)**	**With *STK11* mutation (n=117)**	**P-value**
Asian, Black or African American	13	15	0.5760
White	85	78	
Not reported	27	24	

Source: The Authors (2025)

Table 4 - Mutations in *STK11* and their relation to sex.

Sex	**Without *STK11* mutation (n=125)**	**With *STK11* mutation (n=117)**	**P-value**
Female	42	41	0.8132
Male	83	76	

Source: The Authors (2025)

Next, we evaluated whether patients with mutations in *STK11* have a worse prognosis than other patients. Data of time until death were not available for 80 patients without STK11 mutation and 71 patients with STK11. When analyzing the time from diagnosis to patient death (Table 5), no difference was found between cases with and without *STK11* mutation (0.3432). The majority of cases do not have information, and excluding this group, most had a time to death of less than two years. The lack of information may be due to missing data in the database or because the patient did not pass away yet.

Table 5 - Time until death in patients with *STK11*-mutated lung cancer.

Time until death	**Without *STK11* mutation (n=45)**	**With *STK11* mutation (n=46)**	**P-value**
Less than 2 years	26	31	0.3432
More than 2 years	19	15	

Source: The Authors (2025)

4 DISCUSSION

Lung cancer is responsible for 1.6 million deaths per year, and its epidemiological parameters have been changing over the years. Among the associated factors are the increase in anti-smoking policies and the introduction of filters in cigarettes, which correlate with the rising incidence of adenocarcinoma and a decrease in squamous cell carcinoma (Tsukazan *et al.,* 2017). Despite the progress in studies for the development of new drugs that assist in the treatment of lung cancer, such as immunotherapy and tyrosine kinase inhibitors, it remains one of the most prevalent and deadly cancers worldwide, with a close association with both smokers and non-smokers, with adenocarcinoma being the most common subtype (Gillette *et al.,* 2020).

Furthermore, the majority of diagnoses (70%) are made in advanced or even metastatic stages, while a minority of cases (8%) are attributed to early-stage lung cancer. However, due to limitations in diagnosis and reporting, it is believed that these

numbers may be higher. The present study is in accordance with Mascarenhas *et al*. (2020), where adenomas and adenocarcinomas are the main histological diagnoses with mutations in *STK11*, accounting for 86.32% of the sample size.

In the search for new biomarkers, *STK11* is highlighted. Located in the telomeric region of the short arm of chromosome 19 (19p13.3), it is a tumor suppressor that encodes the liver kinase B1 (LKB1), responsible for activating AMPK and subsequently inhibiting tumor development. However, mutations in *STK11* cause partial loss of AMPK regulation, resulting in abnormal expression of mTOR and HIF-1-alpha, which are related to cell survival and metabolism (Shire *et al.,* 2020). Furthermore, such mutations are associated with negative regulation of programmed death-ligand 1 (PD-L1) expression, lower T-cell infiltration, and reduced benefits from systemic therapy with immune checkpoint inhibitors (ICIs), due to silencing of stimulator of interferon genes (STING) expression (Stinchcombe *et al*., 2023). Xiao *et al*. (2023) also shows that 6% to 13.6% of cases of non-small cell lung cancer (NSCLC) have *STK11* mutations and are associated with an unfavorable prognosis compared to those without the mutation. This study using TCGA data revealed even higher mutation rates in *STK11* (48.35%).

STK11 can undergo numerous genetic variations, such as deletion, insertion, and substitution, with substitution being the most prevalent in this study (76.6% of the analyzed cases), followed by depletion (17.2%) (Mascarenhas *et al*., 2020). In contrast, another cohort study by Gutierrez *et al*. (2022), analyzing 559 patients with non-epidermoid non-small cell lung cancer (NSCLC), identified *STK11* gene mutations in 18.4% of individuals, with 22.5% occurring as single or biallelic deletions. Such deletions affect radiation resistance by activating the KEAP1/NRF2 pathway and upstream NRF2 synthesis while reducing reactive oxygen species (ROS) levels, according to Xiao *et al*. (2023). Similarly, the study by Kouvien *et al*. (2008) found that the majority of *STK11* mutations were deletions or insertions (74%), with the remainder being missense (21%) and nonsense (6%) substitutions.

Substitution mutations can be classified into transition mutations, which involve the same type of base, and transversion mutations, which occur in bases of different types. Missense mutations occur when there is an amino acid substitution, while nonsense mutations result in a stop codon. Nonsense mutations are correlated with an increased risk of tumor development, as individuals in these cases fail to produce the *STK11* protein. However, substitution mutations tend to be less severe because

the genetic code is degenerate. Thus, the substitution of one base in a codon may alter the triplet, but it may not necessarily change the amino acid it encodes, unlike deletions or insertions (Alberts *et al.*, 2017).

As indicated by Mathias *et al*. (2020), lung cancer is the second most common cancer in men and the fourth most common in women, and it remains the leading cause of cancer-related deaths in men and the second leading cause in women. In the present study, there was no sex predominance in *STK11* mutation (Mascarenhas *et al*., 2020). In contrast, studies have reached conflicting conclusions regarding associations between *STK11* genomic alterations and sex. Mitchell *et al*. (2020) proposed a cohort study in which *STK11* expression was higher in women and in never-smokers. On the other hand, Matsumoto *et al*. (2007) found a higher prevalence among males and smokers in their analysis.

Furthermore, STK11 mutations had no relation with ethnicity. Koivunen *et al*. (2008), when evaluating 310 tumor specimens from patients with NSCLC found a higher frequency of *STK11* gene mutation in NSCLC tumors of American origin (17%) compared to Asians (5%). Similarly, the study by Izumi *et al*. (2020), which compared the Cancer Genome Atlas predominantly consisting of Caucasians, with the Japan Molecular Epidemiology for Lung Cancer study involving only Japanese individuals, found a higher mutation rate in the *EGFR* gene among Japanese individuals (14.6% vs. 51.1%) and a higher mutation rate in *STK11* among Caucasians (17.8% vs. 0.7%).

According to Pons-Tonstivint *et al*. (2021), it is evident that the loss of *STK11*/LKB1 promotes the proliferation, motility, and invasion of cancer cells, as well as metastasis. An observational retrospective multicenter study with 201 NSCLC patients associated *STK11* mutations with a negative prognostic (Sposito *et al.*, 2025). Although, in this study patients with *STK11* gene mutation did not had a worse prognosis.

Additionally, Skoulidis *et al*. (2018) demonstrates that alterations in *STK11*/LKB1 are associated with the lack of PD-L1 expression in tumor cells in multiple independent cohorts, a finding consistent with lower densities of infiltrating cytotoxic CD8+ T lymphocytes in human and murine tumors, implying lower efficacy in anti-PD-1 therapy. In addition, a retrospective study with 53 patients with non-squamous NSCLC found that *STK11* mutation in the combined radiation therapy cohort was associated with a 2-year recurrence incidence of 62%, while individuals without the mutation had a recurrence rate of 20% (Katipally *et al*., 2023).

Beyond the CD8+ T lymphocytes impairment, *in vivo* studies of LKB1-deficient tumors have also demonstrated dendritic cell dysfunction (Yao *et al*., 2025). Aligned with these findings, an analysis of 3194 patients with NSCLC treated with chemoimmunotherapy linked *STK11* mutations to a lower response rate to therapy, shorter progression-free survival, and reduced overall survival (Gandhi *et al.,* 2025). Furthermore, a high intratumoral neutrophil-to-lymphocyte ratio, a parameter associated with an immunosuppressed phenotype and worse prognosis across multiple cancers, was found to be more prevalent in *STK11*-mutated NSCLC tumors (Mitchell *et al.,* 2025).

Papillon-Cavanagh *et al*. (2020) states in their study that individuals with mutations in both *STK11* and KEAP1 have a worse prognosis, regardless of the treatment approach, compared to isolated mutations, suggesting an additive effect between the two mutations. It is concluded that *STK11*-KEAP1 mutations may serve as predictive biomarkers for anti-PD-1/PD-L1 therapy, however, they should not be used as patient selection markers.

A key limitation of this study is the reliance on retrospective data from the TCGA database, which contain incomplete clinical records. The sample size for patients with available *STK11* mutation data (n=242) represents only a small subset of the total lung cancer cases, potentially limiting the statistical power and generalizability of the findings. Furthermore, the study does not account for potential confounding factors such as specific treatment regimens, co-mutations, or environmental influences, which could affect prognosis and the observed association between *STK11* mutations and survival.

5 CONCLUSION

Lung cancer with involvement of mutations in the *STK11* gene has been shown to be more associated to adenocarcinomas. The most frequent type of mutation was substitution. Despite the evidence from the literature, the data from TCGA did not allow for a conclusive determination of the real impact of *STK11* mutations on the survival of lung cancer patients after diagnosis. The *STK11* gene is still underexplored in medical practice, and its mutations are strongly associated with tumor development. Considering the high incidence, further investigation of *STK11* as a potential marker of therapeutic response in cancer patients is suggested, as well as the development of

new effective therapies aimed at restoring its function as a tumor suppressor.

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