Distinct Clinicopathological and Prognostic Associations of KCNQ1 Expression in Lung Adenocarcinoma and Lung Squamous Cell Carcinoma

Abstract

KCNQ1 (potassium voltage-gated channel subfamily Q member 1) is a voltage-gated potassium channel subunit involved in the regulation of membrane potential and cellular ion homeostasis. Although ion channels have been increasingly recognized as important regulators of cancer biology, the clinical significance of KCNQ1 expression in non-small cell lung cancer (NSCLC) according to histological subtype remains unclear. This study aimed to investigate the association between KCNQ1 expression and clinicopathological characteristics and overall survival in lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC). RNA sequencing and clinical data of patients with LUAD and LUSC were obtained from The Cancer Genome Atlas (TCGA) database. Patients were divided into high- and low-KCNQ1 expression groups based on the median expression value, and the associations between KCNQ1 expression and clinicopathological variables were analyzed. Overall survival was evaluated using Kaplan–Meier survival analysis. KCNQ1 expression showed different clinical associations according to the histological subtype of NSCLC. In LUSC, patients with high KCNQ1 expression demonstrated significantly poorer overall survival than those with low expression. In contrast, no significant association between KCNQ1 expression and overall survival was observed in LUAD. These findings suggest that the clinical relevance of KCNQ1 expression may differ between LUAD and LUSC. KCNQ1 expression may have subtype-specific clinical relevance, particularly in relation to survival in LUSC, although its independent prognostic significance remains uncertain. Further studies involving tissue-level validation and functional experiments are required to clarify the biological mechanisms underlying the association between KCNQ1 expression and NSCLC progression.

Keywords: KCNQ1; non-small cell lung cancer; lung adenocarcinoma; lung squamous cell carcinoma; TCGA

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1. Introduction

Lung cancer remains one of the leading causes of cancer-related mortality worldwide and is the second most commonly diagnosed cancer globally [1]. Based on histopathological characteristics, lung cancer is broadly classified into non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC accounts for more than 85% of all lung cancer cases and is primarily composed of lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC), the two major histological subtypes [2].

Although both LUAD and LUSC are classified as NSCLC, they differ considerably in their molecular alterations, biological behavior, and clinical outcomes. These differences have highlighted the importance of identifying subtype-specific biomarkers that improve prognostic stratification and clinical management [3]. Despite advances in targeted therapy and immunotherapy, the overall prognosis of patients with NSCLC remains poor, with long-term survival rates below 20% [4,5]. Therefore, the identification of reliable prognostic biomarkers remains an important clinical challenge.

Ion channels have emerged as important regulators of cancer biology and have been implicated in cell proliferation, migration, apoptosis, and tumor progression [6,7]. KCNQ1 encodes a voltage-gated potassium channel that is expressed in multiple epithelial tissues, including the lung [8]. Although KCNQ1 has been extensively studied in inherited cardiac disorders, accumulating evidence suggests that altered KCNQ1 expression is associated with tumor development and progression in several malignancies, including colorectal, hepatocellular, esophageal, and renal cancers [8–14].

However, the clinicopathological and prognostic significance of KCNQ1 expression in NSCLC remains unclear, particularly with respect to histological subtype [15]. Previous studies have demonstrated substantial molecular differences between LUAD and LUSC, indicating that the clinical relevance of individual biomarkers may vary according to tumor histology [15–19]. Differences in lineage-specific molecular backgrounds and downstream signaling networks may contribute to such subtype-dependent associations. Nevertheless, whether KCNQ1 exhibits distinct clinicopathological associations and survival-related associations in these two major NSCLC subtypes has not been systematically evaluated.

Therefore, this study investigated the associations between KCNQ1 expression and clinicopathological characteristics, as well as its prognostic significance, in LUAD and LUSC using The Cancer Genome Atlas (TCGA) dataset. By comparing these two major histological subtypes, we sought to determine whether the clinical significance of KCNQ1 differs according to histological context.

2. Materials and Methods

2.1. TCGA Data Acquisition and Processing

Gene expression data and corresponding clinical information were obtained from The Cancer Genome Atlas (TCGA) database. A total of 980 patients with non-small cell lung cancer (NSCLC) were included, comprising 492 patients with lung adenocarcinoma (LUAD) and 488 patients with lung squamous cell carcinoma (LUSC). KCNQ1 mRNA expression data and clinicopathological variables, including age, sex, pathologic T, N, and M categories, EGFR mutation status (when available), and smoking history, were retrieved for analysis. Variables with missing or unknown information were retained as missing/unknown categories where applicable and were excluded from the corresponding analysis when information was unavailable. Because TCGA data are publicly available and de-identified, institutional review board approval and informed consent were not required.

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2.2. Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). Patients were classified into high- and low-expression groups according to the median KCNQ1 mRNA expression level within each histological subtype. The median was selected as the cut-off to provide a predefined and balanced classification of patients into high- and low-expression groups within each histological subtype. Associations between KCNQ1 expression and clinicopathological characteristics were evaluated using chi-square test or Fisher's exact test, as appropriate, particularly when expected cell counts were small. Overall survival (OS) was analyzed using the Kaplan–Meier method, and differences between survival curves were assessed using the log-rank test. All statistical tests were two-sided, and a P value < 0.05 was considered statistically significant.

3. Results

3.1. Relationship between KCNQ1 Expression Levels and Clinicopathological Variables in Non-Small Cell Lung Cancer (NSCLC)

To investigate the relationship between KCNQ1 expression and clinicopathological characteristics, patients were classified into high- and low-expression groups according to the median KCNQ1 mRNA expression level. Analyses were performed separately for patients with lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC). In the LUAD cohort (Table 1), KCNQ1 expression was significantly associated with nodal status ($P = 0.012$). Among patients with lymph node metastasis (N1–N3), the proportion of patients with high KCNQ1 expression was lower than that of patients with low expression (41.1% vs. 58.9%). In contrast, among patients without lymph node metastasis (N0), high KCNQ1 expression was slightly more frequent than low expression (53.1% vs. 46.9%). Although the association did not reach statistical significance, the proportion of tumors with high KCNQ1 expression tended to decrease with increasing T category ($P = 0.084$).

In the LUSC cohort (Table 2), no significant associations were observed between KCNQ1 expression and any clinicopathological variables, including age, sex, pathologic T, N, and M categories, EGFR mutation status, or smoking history (all $P > 0.05$). Although the frequency of high KCNQ1 expression was lower in T4 tumors than in lower T categories, this difference was not statistically significant ($P = 0.163$).

3.2. Prognostic Value and Survival Analysis of KCNQ1 Expression in NSCLC

The prognostic significance of KCNQ1 expression was evaluated using Kaplan–Meier survival analysis. In the LUAD cohort, patients with high KCNQ1 expression exhibited significantly better overall survival than those with low expression ($P = 0.004$; Figure 1A). In contrast, patients with high KCNQ1 expression in the LUSC cohort showed significantly poorer overall survival than those with low expression ($P = 0.040$; Figure 1B). These findings demonstrate that the prognostic association of KCNQ1 expression differs between the two major histological subtypes of NSCLC.

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Table 1. Clinical characteristics of KCNQ1 expression in lung adenocarcinoma (LUAD)

	KCNQ1 Expression		P Value
	High (%, N)	Low (%, N)	
Age			0.191
≤65 years	47.0 (111)	53.0 (125)	
≥65 years	52.9 (135)	47.1 (120)	
Sex			0.526
Male	48.4 (109)	51.6 (116)	
Female	51.3 (137)	48.7 (130)	
T stage			0.084
T1	57.2 (95)	42.8 (71)	
T2	46.9 (122)	53.1 (138)	
T3	46.7 (21)	53.3 (24)	
T4	33.3 (6)	66.7 (12)	
N stage			0.012
N0	53.1 (169)	46.9 (149)	
≥N1	41.1 (67)	58.9 (96)	
M stage			0.715
M0	49.7 (161)	50.3 (163)	
M1	45.8 (11)	54.2 (13)	
EGFR mutation			0.313
(+)	44.8 (13)	55.2 (16)	
(-)	54.9 (101)	45.1 (83)	
Smoking status			0.498
Yes	49.0 (164)	51.0 (171)	
No	52.2 (82)	47.8 (75)	

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Table 2. Clinical characteristics of KCNQ1 expression in lung squamous cell carcinoma (LUSC)

	KCNQ1 Expression		P Value
	High (%, N)	Low (%, N)	
Age			0.926
≤65 years	50.3 (95)	49.7 (94)	
≥65 years	49.8 (149)	50.2 (150)	
Sex			0.098
Male	47.8 (173)	52.2 (189)	
Female	56.3 (71)	43.7 (55)	
T stage			0.163
T1	56.0 (61)	44.0 (48)	
T2	49.3 (141)	50.7 (145)	
T3	50.0 (35)	50.0 (35)	
T4	30.4 (7)	69.6 (16)	
N stage			0.226
N0	52.4 (163)	47.6 (148)	
≥N1	46.2 (79)	53.8 (92)	
M stage			0.752
M0	48.9 (196)	51.1 (205)	
M1	42.9 (3)	57.1 (4)	
EGFR mutation			0.409
(+)	61.9 (13)	38.1 (8)	
(-)	50.0 (136)	50.0 (136)	
Smoking status			0.900
Yes	49.9 (206)	50.1 (207)	
No	50.7 (38)	49.3 (37)	

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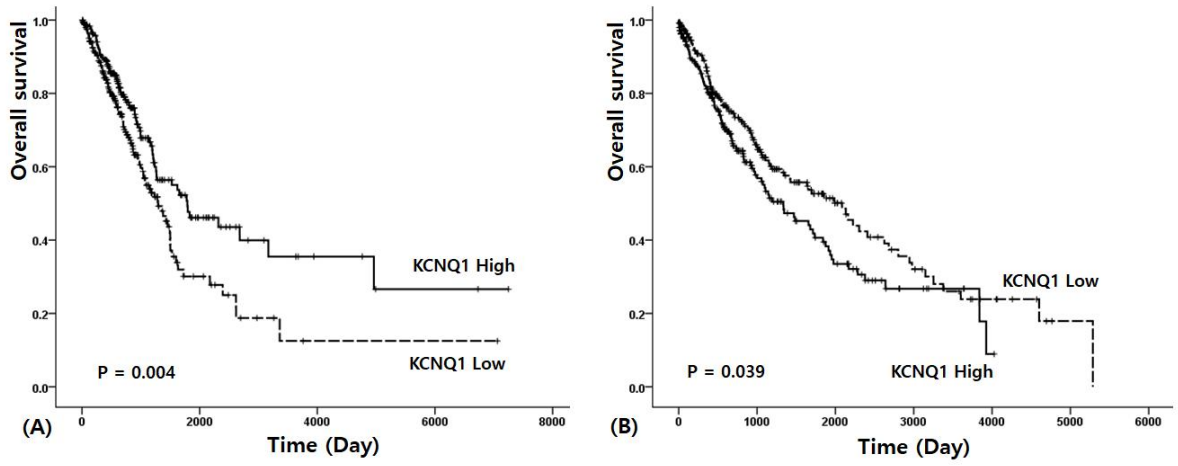


Figure 1. Kaplan–Meier survival curves according to KCNQ1 expression in lung adenocarcinoma (A) and lung squamous cell carcinoma (B).

4. Discussion

In the present study, we investigated the association between KCNQ1 (potassium voltage-gated channel subfamily Q member 1) expression and clinicopathological characteristics and overall survival in the two major histological subtypes of non-small cell lung cancer (NSCLC), lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC). Our results demonstrated that higher KCNQ1 expression was significantly associated with poorer overall survival in patients with LUSC, whereas no significant survival difference was observed in LUAD. These findings suggest that the clinical relevance of KCNQ1 expression may differ according to the histological subtype of NSCLC.

Lung cancer represents a heterogeneous group of malignancies with distinct morphological and molecular characteristics depending on histological subtype. LUAD and LUSC, the two major subtypes of NSCLC, differ in their cellular origins, differentiation patterns, genomic alterations, and clinical behaviors [2,3,16,19]. LUAD frequently exhibits various driver mutations and has benefited from the development of targeted therapies, whereas LUSC is strongly associated with smoking-related carcinogenesis and squamous differentiation, with relatively limited therapeutic options in advanced disease [20-22]. Therefore, identification of molecular markers associated with biological characteristics and clinical outcomes is particularly important for understanding LUSC progression.

KCNQ1 is a voltage-gated potassium channel subunit that plays an important role in regulating membrane potential and maintaining cellular ion homeostasis [12,14]. Although potassium channels were initially recognized primarily for their physiological functions in excitable tissues, accumulating evidence indicates that ion channels also contribute to diverse cellular processes, including proliferation, migration, apoptosis, and

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tumor development [7,23,24]. Alterations in potassium channel expression may influence membrane excitability and intracellular signaling pathways, thereby affecting the biological behavior of cancer cells [23,24].

Previous studies have suggested that KCNQ1 may be involved in tumor-related processes. A multi-omic analysis demonstrated that KCNQ1 may have potential theragnostic relevance in lung adenocarcinoma [8]. In addition, KCNQ1 has been implicated in the progression of other malignancies through regulatory mechanisms involving microRNAs and downstream signaling pathways [10,11]. However, the clinical significance of KCNQ1 expression according to histological subtype in NSCLC remains insufficiently understood.

In the present study, the association between high KCNQ1 expression and unfavorable survival outcomes was observed specifically in LUSC. This finding suggests that KCNQ1 expression may reflect subtype-specific biological characteristics associated with LUSC progression. Since LUSC exhibits distinct molecular features and differentiation programs compared with LUAD [16,20,21], the biological consequences of altered KCNQ1 expression may vary depending on the cellular context. Such differences may involve subtype-specific regulatory networks or downstream signaling pathways in which KCNQ1 participates. In addition to its canonical role as a potassium channel subunit, KCNQ1 may influence cellular behavior through interactions with other molecular regulators and non-canonical signaling pathways. However, these possibilities remain hypothetical in the context of the present study and cannot be directly evaluated using TCGA transcriptomic and clinical data alone. The absence of a significant survival association in LUAD despite the observed association in LUSC may also reflect differences in the molecular background of the two histological subtypes. LUAD and LUSC are characterized by different patterns of genetic alterations, cellular differentiation, and signaling activity, which may modify the biological consequences of KCNQ1 expression. Therefore, the prognostic association observed in LUSC should not necessarily be extrapolated to LUAD [25,26]. Further studies integrating KCNQ1 with subtype-specific molecular alterations and downstream signaling pathways may help clarify the basis of this differential association. However, because this study was based on transcriptomic and clinical data obtained from TCGA, the functional role of KCNQ1 in tumor progression cannot be directly determined. Further experimental studies are required to clarify whether KCNQ1 actively contributes to LUSC progression or represents a molecular marker associated with specific tumor characteristics.

Overall, our findings indicate that KCNQ1 expression has different clinical implications between LUAD and LUSC. Although KCNQ1 expression was not significantly associated with survival outcomes in LUAD, its association with poor overall survival in LUSC suggests that KCNQ1 may have subtype-specific clinical relevance. Further investigations involving tissue-level expression analysis and functional validation are necessary to elucidate the biological mechanisms underlying the subtype-dependent association of KCNQ1.

Several limitations should be acknowledged. First, this study was based on publicly available TCGA transcriptomic data, and independent clinical specimens for protein-level validation were not available [27]. Second, survival analysis was performed using Kaplan–Meier and log-rank tests without multivariable adjustment; therefore, potential confounding factors such as smoking status and pathological stage could not be independently controlled, and the observed association should not be interpreted as evidence of an independent

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prognostic effect of KCNQ1. Finally, the retrospective transcriptomic design does not allow causal or functional conclusions regarding the role of KCNQ1 in NSCLC. Further studies using independent clinical cohorts, protein-level validation, and functional experiments are warranted.

In conclusion, KCNQ1 expression showed a subtype-dependent association with overall survival in NSCLC, with higher expression associated with poorer survival in LUSC but not in LUAD. These findings suggest that the clinical relevance of KCNQ1 may differ according to histological subtype. Further validation is required to determine the biological basis and clinical significance of this association.

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