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Gene mutation in diabetic patients with lung adenocarcinoma: a real-world retrospective cohort study

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Purpose: The incidence of lung cancer is closely associated with diabetes; however, it remains unclear whether diabetes influences the genetic mutations present in lung cancer. Therefore, we will compare the genetic mutations in patients with lung adenocarcinoma (ADC) who have diabetes against those who do not.

Methods: We included 279 patients diagnosed with lung adenocarcinoma (143 with diabetes and 136 without diabetes) at the Second Affiliated Hospital of Chongqing Medical University between 2016 and 2023, and analyzed the clinical characteristics and genetic mutation profiles of all participants.

Results: In comparison to ADC patients without diabetes, those with diabetes exhibited a lower overall gene mutation rate (49.7% vs. 65.4%, $P = 0.008$). Female ADC patients demonstrated a higher total gene mutation rate and EGFR gene mutation rate than their male counterparts (49.3% vs. 66.9%, $P = 0.003$; 27.6% vs. 58.3%, $P < 0.001$, respectively), although their TP53 gene mutation rate was lower (8.6% vs. 2.4%, $P = 0.027$). ADC patients without a smoking history had a higher gene mutation rate and EGFR gene mutation rate than those with a smoking history (62.6% vs. 47.4%, $P = 0.014$; 51.6% vs. 22.7%, $P < 0.001$, respectively), but a lower KRAS gene mutation rate (4.4% vs. 14.4%, $P = 0.003$). Conversely, ADC patients with a drinking history had a lower EGFR gene mutation rate than those without (48% vs. 62.6%, $P = 0.018$; 31.0% vs. 47.5%, $P = 0.007$), yet a higher KRAS gene mutation rate (14.0% vs. 4.5%, $P = 0.005$). Univariate and multivariate linear regression analyses revealed that being female, having no smoking history, and being in phase II or IV of tumor stage were associated with gene mutation. Subgroup analysis indicated that the rate of gene mutation in male smoking lung adenocarcinoma patients with diabetes was significantly lower than in those without diabetes.

Conclusion: This retrospective study of real-world data suggests that patients with lung adenocarcinoma and diabetes may have a reduced likelihood of developing genetic mutations, particularly among male smokers. Furthermore, gender, smoking history, and tumor stage may be correlated with the presence of gene mutations.

KEYWORDS

lung adenocarcinoma, gene mutations, diabetes, smoking, drinking

Introduction

Lung cancer stands as the second most prevalent form of malignant cancer, responsible for 11.4% of all new cancer diagnoses. It remains the primary cause of cancer-related mortality, with an estimated 1.8 million fatalities annually (1). Lung adenocarcinoma (ADC) has emerged as the predominant cell type among lung cancer cases globally (2). Interestingly, East Asians who have never smoked are more frequently diagnosed with adenocarcinoma, a subtype characterized by specific oncogenic drivers. The discovery of activating epidermal growth factor receptor (EGFR) mutations, which respond to EGFR tyrosine kinase inhibitors (TKIs), was initially made in Asian women and non-smokers with lung adenocarcinoma (3–5). As high-throughput sequencing technology has progressed, the molecular landscape of lung cancer has unveiled a spectrum of carcinogenic factors. Consequently, genetic testing is now advised for all patients newly diagnosed with non-small cell lung cancer (NSCLC), encompassing mutations in EGFR, anaplastic lymphoma kinase (ALK), ROS proto-oncogene 1 (ROS1), Rearranged during transfection (RET), B-Raf proto-oncogene, serine/threonine kinase (BRAF) V600E, and MET exon 14 skipping mutations. Additionally, the testing should include the evaluation of gene amplifications or overexpression's, such as those in MET, human epidermal growth factor receptor 2 (HER2), Kirsten rat sarcoma viral oncogene homolog (KRAS), and NeuroTrophin Receptor Kinase (NTRK) (6–8).

Diabetes mellitus (DM), the most prevalent metabolic disorder, is characterized by chronically elevated blood glucose levels. This condition manifests in two distinct pathological forms: type 1 diabetes (T1DM) and type 2 diabetes (T2DM). Research has established a bidirectional relationship between diabetes and cancer, with type 2 diabetes in particular being associated with a heightened risk of developing cancer (9). Among the various types of cancer, lung cancer is the most frequent in individuals with type 2 diabetes, with adenocarcinoma being the predominant form (10). Irrespective of the diabetes type, elevated blood glucose can precipitate a range of pulmonary complications, including asthma, chronic obstructive pulmonary disease (COPD), pneumonia, fibrosis, and lung cancer (LC) (11). Multiple potential mechanisms, such as hyperglycemia, hyperinsulinemia, glycation, inflammation, and hypoxia, have been proposed as possible connections between DM and LC (12).

DM is linked to numerous genetic mutations in disease-causing genes. Research has indicated that diabetes appears to elevate the risk of BRAF mutations in patients with colorectal cancer, a condition typically associated with a poor prognosis (13). Furthermore, patients with bone marrow syndrome who also have diabetes exhibit a higher mutation rate of the 10-11 translocation 2 (TET2) and splicing factor 3b subunit 1 gene (SF3B1), which correlates with a more severe prognosis (14). Another study has confirmed that diabetes can dynamically influence tuberculosis (TB) drug resistance genes (15).

However, the impact of diabetes on gene mutation in patients with lung adenocarcinoma remains uncertain. The primary objective of this study was to investigate whether there exist any differences in tumor gene mutations between lung adenocarcinoma patients with diabetes and those without diabetes. Secondary objectives encompass identifying the ways in which various diabetes medications interact with genetic mutations in patients diagnosed with lung adenocarcinoma. To delve into these distinctions, we gathered and analyzed data from 279 patients who had been pathologically diagnosed with lung adenocarcinoma and had undergone genetic testing.

Materials and methods

Subject investigated

A retrospective analysis was conducted on patients with lung adenocarcinoma diagnosed by the Department of Respiratory Medicine, Oncology, and Thoracic Surgery between 2016 and 2023. The duration of diabetes ranged from 1 to 20 years, and all patients were diagnosed of type 2 diabetes and exhibited mild symptoms. The inclusion criteria were as follows: (1) Age of 18 years or older; (2) Pathological diagnosis of lung adenocarcinoma; (3) Completion of tumor gene testing; (4) A history of diabetes, with or without; (5) Diagnosis of diabetes preceding that of lung adenocarcinoma. The exclusion criteria were: (1) Age younger than 18 years; (2) Incomplete tumor genetic testing, as shown in Figure 1. All participants provided signed informed consent forms.

Mutation gene

All genes were subjected to testing and analysis using Next-generation sequencing (NGS), a process conducted in China. The study encompassed commonly mutated genes in lung adenocarcinoma, including EGFR, KRAS, ALK, MET, BRAF, HER2, Tumor Protein 53 (TP53), phosphoinositide 3-kinase (PIK3), and avian Erythroblastosis oncogene B 2 (ERBB2).

Statistical method

The analysis of ordinal variables utilized the median as the primary measure of central tendency. For the examination of categorical variables, the chi-square test or Fisher's exact test was chosen as the preferred method. To assess continuous variables, both the Mann–Whitney *U*-test and the independent samples *T*-test were employed. In order to identify with a high degree of certainty the factors influencing gene mutations, both univariate and multivariate ordinal linear regression analyses were conducted. The statistical computations were performed using SPSS 26 software, which is an offering of IBM Corp. located in Armonk, NY, USA. Additionally, GraphPad Prism (version 9.5.1) was utilized for plotting purposes. A *P* value of less than 0.05 was deemed indicative of a statistically significant difference.

Results

General situation and basic characteristics

This study compiled a total of 279 cases, comprising 143 ADC patients with diabetes and 136 ADC patients without diabetes. As presented in Table 1, no significant disparities were observed

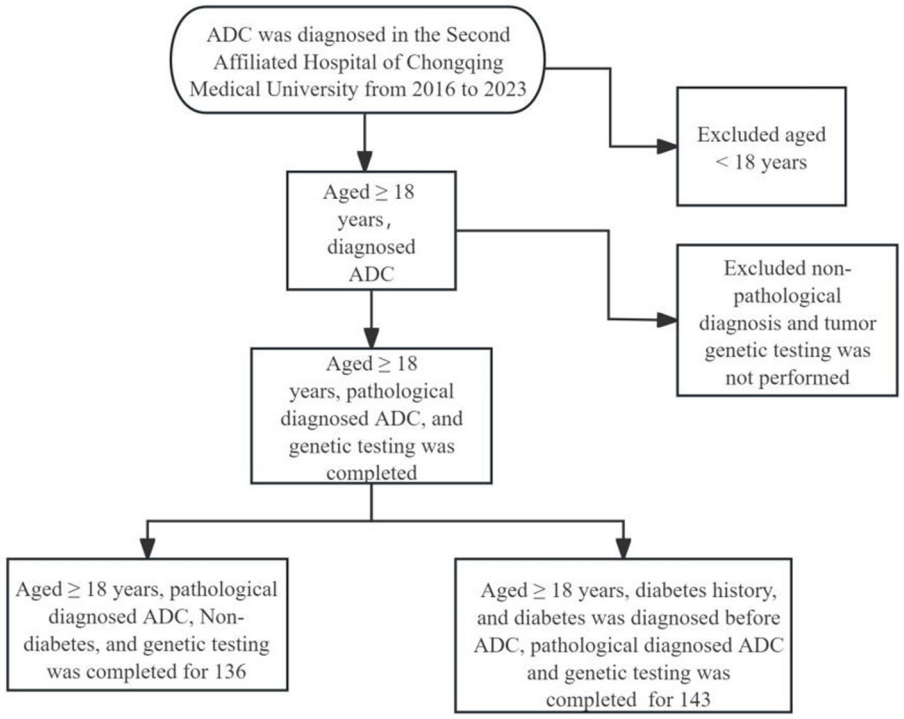

FIGURE 1
Flowchart of participant selection. ADC, lung adenocarcinoma.

in gender, alcohol consumption history, hemoglobin levels, leukocyte count, creatinine levels, alanine aminotransferase (ALT), aspartate aminotransferase (AST), carcinoembryonic antigen (CEA), cytokeratin 19 fragments (CYFRA211), and neuron-specific enolase (NSE) between the ADC patients with diabetes and the control group. However, the ADC patients with diabetes exhibited a higher median body mass index (BMI) (23.19 vs. 21.77, $P < 0.001$) and lower platelet counts (210 vs. 236, $P = 0.029$). Additionally, notable differences were identified in the clinical stage and nodule characteristics between the two groups.

Gene mutation characteristics for all participators

ADC patients with DM exhibited a lower total gene mutation rate compared to those without DM (49.7% vs. 65.4%, $P = 0.008$), as indicated in Table 2. Among female ADC patients, the gene mutation rate and EGFR gene mutation rate were higher than in male patients (49.3% vs. 66.9%, $P = 0.003$; 27.6% vs. 58.3%, $P < 0.001$, respectively). However, the TP53 gene mutation rate was lower in females (8.6% vs. 2.4%, $P = 0.027$), as detailed in Table 3. ADC patients without a smoking history had a higher gene mutation rate and EGFR gene mutation rate than those with a smoking history (62.6% vs. 47.4%, $P = 0.014$; 51.6% vs. 22.7%, $P < 0.001$, respectively), but a lower KRAS gene mutation rate (4.4% vs. 14.4%, $P = 0.003$), as presented in Table 4. Conversely, ADC patients with a drinking history had a lower gene mutation rate and EGFR gene mutation rate than those without a drinking history (48% vs. 62.6%, $P = 0.018$; 31.0% vs. 47.5%, $P = 0.007$), yet a higher KRAS gene mutation rate (14.0% vs. 4.5%, $P = 0.005$), as outlined in Table 5.

Univariate and multivariate analysis

Upon conducting univariate and multivariate regression analyses, we determined that gender, smoking history, and clinical stage were independent risk factors for genetic mutations in ADC patients with diabetes, with a significance level of $P < 0.05$ as shown in Table 6.

Subgroup analysis

In further subgroup analysis, for the patient population with ADC among male smokers, we observed a reduced rate of gene mutation patients with diabetes compared to those without diabetes ($P = 0.019$) (Figure 2A) shows, which is no difference in other subgroups (Figures 2B–D).

Discussion

In this retrospective study, we examined the prevalence of common mutated genes in lung adenocarcinoma. We assessed variations in gene mutation rates among patients with lung adenocarcinoma, stratified by the presence or absence of diabetes,

TABLE 1 General characteristics of all the participants.

Various	ADC patients with diabetes ($n = 143$)	ADC patients without diabetes ($n = 136$)	*P*-value	*P*-value*
Age (years) mean (SD) median (Min-Max)	67.57 (8.89) 68.00 (40.00–86.00)	65.66 (8.85) 66.00 (45.00–91.00)	0.074	0.076
BMI (Kg/m^2) mean (SD) median (Min-Max)	23.36 (3.01) 23.19 (15.82–30.30)	22.00 (3.07) 21.77 (13.78–31.11)	<0.001	<0.001
HB (g/L) mean (SD) median (Min-Max)	121.88 (16.71) 123.00 (87.00–169.00)	123.70 (18.29) 126.00 (61.00–172.00)	0.387	0.210
WBC (10∧9/L) mean (SD) median (Min-Max)	7.02 (2.22) 6.60 (2.89–15.81)	6.82 (1.88) 6.69 (3.49–13.42)	0.423	0.807
PLT (10∧9/L) mean (SD) median (Min-Max)	220.69 (85.38) 210.00 (25.00–511.00)	243.85 (91.02) 235.50 (11.00–485.00)	0.029	0.025
AST (IU/L) mean (SD) median (Min-Max)	21.23 (14.19) 17.00 (4.00–115.00)	19.60 (12.01) 17.00 (6.00–81.00)	0.301	0.347
ALT (IU/L) mean (SD) median (Min-Max)	24.09 (25.99) 19.00 (4.00–269.00)	21.92 (8.76) 20.50 (8.00–60.00)	0.355	0.416
CR(μmol/L) mean (SD) median (Min-Max)	70.92 (46.04) 63.10 (5.90–418.80)	65.68 (17.23) 63.05 (30.50–130.60)	0.213	0.957
Carcinoembryo nic antigen mean (SD) median (Min-Max)	89.86 (214.11) 7.92 (0.41–1000.00)	66.18 (180.92) 7.47 (0.23–1000.00)	0.320	0.397
Cytokeratin 19 fragments mean (SD) median (Min-Max)	5.65 (7.25) 3.21 (0.15–58.91)	7.77 (14.51) 3.08 (0.76–100.00)	0.121	0.745
Neuron-specific enolase mean (SD) median (Min-Max)	15.18 (6.63) 13.91 (7.29–65.81)	17.19 (11.78) 13.98 (1.90–84.56)	0.078	0.492
Sex				
Male	82 (57.34%)	70 (51.47%)	0.325	
Female	61 (42.66%)	66 (48.53%)		
Smoking history				
Yes	43 (30.07%)	54 (39.71%)	0.091	
No	100 (69.93%)	82 (60.29%)		
Drinking history				
Yes	59 (41.26%)	41 (30.15%)	0.053	
No	84 (58.74%)	95 (69.85%)		
Tumor location				
Up left	35 (24.48%)	31 (22.79%)	0.348	
Low left	28 (19.58%)	24 (17.65%)		
Upper right	44 (30.77%)	40 (29.41%)		

(Continued)

TABLE 1 (Continued)

Various	ADC patients with diabetes ($n = 143$)	ADC patients without diabetes ($n = 136$)	*P*-value	*P*-value*
Center right	14 (9.79%)	7 (5.15%)		
Low right	18 (12.59%)	29 (21.32%)		
Hilus of the lung	4 (2.80%)	5 (3.68%)		
Nodule property				
Solid nodules	121 (84.62%)	130 (95.59%)	0.002	<0.001
Ground glass nodules	17 (11.89%)	2 (1.47%)		
Mixed nodules	5 (3.50%)	4 (2.94%)		
Clinical stages				
I	36 (25.17%)	9 (6.62%)	<0.001	
II	7 (4.90%)	4 (2.94%)		
III	10 (6.99%)	13 (9.56%)		
IV	90 (62.94%)	110 (80.88%)		

*Presented as Median (Range). For categorical variables, Fisher's Exact Test and the Chi-Square Test of Independence were employed, whereas for continuous variables, the Mann-Whitney *U*-Test and the *T*-Test were utilized.

TABLE 2 Comparison of gene mutations in ADC patients with or without diabetes.

	ADC patients with diabetes ($n = 143$)	ADC patients without diabetes ($n = 136$)	*P*-value
Total gene mutation rate (%)	49.7% (71/143)	65.4% (89/136)	0.008
EGFR (%)	37.8% (54/143)	45.6% (62/136)	0.185
ALK (%)	1.4% (2/143)	4.4% (6/136)	0.164
KRAS (%)	7.7% (11/143)	8.1% (11/136)	0.902
MET (%)	2.1% (3/143)	/	1
BRAF (%)	0.7% (1/143)	1.5% (2/136)	1
HER2 (%)	0.7% (1/143)	1.5% (2/136)	1
TP53 (%)	4.2% (6/143)	7.35% (10/136)	0.257
PTK3 (%)	0.7% (1/143)	1.5% (2/136)	1
ERBB2 (%)	1.4% (2/143)	1.5% (2/136)	1

Fisher's exact test and the Chi-Square statistic test were utilized.

TABLE 3 Comparison of gene mutation in ADC patients of different gender.

	ADC patients (male)	ADC patients (female)	*P*
Total gene mutation rate (%)	49.3% (75/152)	66.9% (85/127)	0.003
EGFR (%)	27.6% (42/152)	58.3% (74/127)	< 0.001
ALK (%)	2.6% (4/152)	3.1% (4/127)	1
KRAS (%)	9.9% (15/152)	5.5% (7/127)	0.179
MET (%)	1.3% (2/152)	0.8% (1/127)	1
BRAF (%)	1.3% (2/152)	0.8% (1/127)	1
HER2 (%)	2.0% (3/152)	/	1
TP53 (%)	8.6% (13/152)	2.4% (3/127)	0.027
PIK3 (%)	1.3% (2/152)	0.8% (1/127)	1
ERBB2 (%)	1.3% (2/152)	1.6% (2/127)	1

Fisher's exact test and the Chi-Square statistic test were utilized.

smoking history, alcohol consumption, and gender. Our findings indicate that patients with diabetes exhibited a lower rate of gene mutations. Furthermore, these mutations were associated with sex, smoking history, and the stage of the tumor.

Cancer is progressively emerging as the leading cause of mortality globally, with annual projections indicating a surge in both new cases and fatalities (16). An ever-growing body of evidence underscores a direct link between diabetes and cancer, particularly in the context of several of the most prevalent malignant tumors. Prior research has revealed lung cancer as the most frequent malignant tumor that is complicated by diabetes (17). The activation of the oncogene KRAS2, the deactivation of the tumor suppressor gene (Recombinant Cyclin Dependent Kinase Inhibitor 2A, CDKN2A), the silencing of the tumor suppressor TP53, and the mutation of the pancreatic cancer-related gene 4 (DPC4), which holds a pivotal role in pancreatic carcinogenesis, are all intimately associated with a poor prognosis in patients diagnosed with pancreatic cancer. Strikingly, an astonishing 80% of these patients concurrently grapple with diabetes, a figure that underscores the intricate interplay between these genetic mutations and metabolic disturbances (18). Concurrently, patients with colorectal cancer harboring BRAF mutations typically exhibit a poor prognosis, and diabetes further elevates the risk of such mutations (13). In individuals with bone marrow syndrome, mutations in TET2 and SF3B1 genes are associated with a more severe prognosis, and the presence of diabetes also amplifies the

TABLE 4 Comparison of gene mutation in ADC patients with or without smoking history.

	ADC patients without smoking history	ADC patients with smoking history	*P*-value
Total gene mutation rate (%)	62.6% (114/182)	47.4% (46/97)	0.014
EGFR (%)	51.6% (94/182)	22.7% (22/97)	<0.001
ALK (%)	3.3% (6/182)	2.1% (2/97)	0.718
KRAS (%)	4.4% (8/182)	14.4% (14/97)	0.003
MET (%)	0.5% (1/182)	2.1% (2/97)	1
BRAF (%)	1.1% (2/182)	1.0% (1/97)	1
HER2 (%)	/	3.1% (3/97)	1
TP53 (%)	6.0% (11/182)	5.6% (5/97)	0.761
PTK3 (%)	1.6% (3/182)	/	1
ERBB2 (%)	1.6% (3/182)	1.0% (1/97)	1

Fisher's exact test and the Chi-Square statistic test were utilized.

TABLE 5 Comparison of gene mutation in ADC patients with or without drinking history.

	ADC patients with drinking history	ADC patients without drinking history	*P*-value
Total gene mutation rate (%)	48.0% (48/100)	62.6% (112/179)	0.018
EGFR (%)	31.0% (31/100)	47.5% (85/179)	<0.001
ALK (%)	2.0% (2/100)	3.4% (6/179)	0.716
KRAS (%)	14.0% (14/100)	4.5% (8/179)	0.005
MET (%)	1.0% (1/100)	1.1% (2/179)	1
BRAF (%)	1.0% (1/100)	1.1% (2/179)	1
HER2 (%)	2.0% (2/100)	0.6% (1/179)	1
TP53 (%)	7.0% (7/100)	5.0% (9/179)	0.497
PTK3 (%)	/	1.7% (3/179)	1
ERBB2 (%)	1.0% (1/100)	1.7% (3/179)	1

Fisher's exact test and the Chi-Square statistic test were utilized.

frequency of these genetic alterations (14). In our study, the overall gene mutation rate among ADC patients with diabetes was found to be lower (49.7% vs. 65.4%, $P = 0.008$). Moreover, male smokers diagnosed with lung adenocarcinoma and diabetes presented a reduced rate of gene mutations compared to their non-diabetic counterparts (33.3% vs. 57.7%, $P = 0.019$). Consequently, we deduce that the decreased gene mutation rate in patients with diabetes and lung adenocarcinoma may be influenced by a multitude of factors, encompassing genetic predispositions, environmental influences, pharmacological interventions, and immune system status.

However, no significant difference was observed in the mutation rate of individual genes, which contradicts findings from previous studies. This discrepancy may be attributed to the limited sample size of our research or to factors such as smoking habits and gender. The primary risk factors for lung cancer include smoking, yet it is crucial to consider other factors due to the rising incidence of lung cancer in non-smokers (LCINS) (19, 20). Numerous studies (21–23) have indicated a higher prevalence of EGFR mutations in lung cancer patients who have never smoked. Conversely, KRAS mutations are notably more common in patients with a history of tobacco use, and these mutations are often associated with resistance to EGFR-tyrosine kinase inhibitors (24). These results indicate that the two carcinogenic mutations are mutually exclusive. Women have a higher risk of developing lung cancer, especially in lung adenocarcinoma (25). Our research aligns demonstrating that women have significantly greater odds of exhibiting an EGFR mutation in lung tumor tissue compared to men. Previous studies by Chapman and Dang (26, 27) have also corroborated this result, suggesting that women are at a higher risk for lung cancer mutations. According to a study in the Cell that the East Asian EGFR mutation rate was 85%, with a female majority, meanwhile, further analysis of the genetic variants by different sex and smoking status revealed that besides the expected mutual exclusivity between EGFR and KRAS mutations, the RNA-binding motif protein 10(RBM 10) mutations together with the TP53, KRAS, xin actin-binding repeat containing 2(XIRP 2), and zinc finger protein 804B(ZNF804B) mutations were also mutually exclusive. The presence of these mutation exclusivity with high mutation frequency may indicate new synthetic lethality between them or the presence of unique clonal evolution (28–30). Despite the significantly higher prevalence of EGFR mutations in female non-smokers and in patients with women-predominant non-small cell lung cancer (NSCLC), it has been suggested that restricting screenings to only never-smoking women would overlook 57% of all EGFR mutations. The primary reason for this is that a significant percentage of EGFR mutations are found in male patients and smokers, suggesting a broader distribution than previously thought (31). TP53 is linked to the prognosis of lung tumors, and its mutations are indicative of a poor prognosis. Previous studies (32) have indicated that TP53 mutations were present in 125 cases and were significantly correlated with male gender. Our study yielded consistent results, suggesting that the prognosis for male lung adenocarcinoma patients may be less favorable. Furthermore, our findings indicate that lung adenocarcinoma patients with a history of alcohol consumption have a lower rate of EGFR mutations and a higher rate of KRAS mutations. However, factor analysis did not reveal a correlation between alcohol consumption history and gene mutations. Interestingly, our results align with those of studies on smoking history, leading us to suspect that a large proportion of the Chinese population has a history of both smoking and drinking.

The relationship between gene mutations and tumor stage is complex. Previous research has confirmed that EGFR mutations are found in all stages of NSCLC (33). Mutations within exons E18 to E21 were frequently observed in patients diagnosed with lung cancer at stages IA, IB, IIA, and IIB, respectively. Notably, the incidence of KRAS gene mutations in exon E2 was elevated in both whole blood and tissue specimens compared to other exon mutations. Additionally, a significant increase in the frequency of KRAS gene mutations was noted in patients with stage IIB lung cancer within exon E2, and in those with stage IA lung cancer

TABLE 6 Univariate and multivariate analysis of ADC patients with diabetes.

	Univariate OR (95% CI)	*P* value	Multivariate OR (95% CI)	*P* value
Age (years)	1.017 (0.980, 1.056)	0.368	1.038 (0.982, 1.098)	0.184
Gender (female)	1.933 (0.987, 3.787)	0.055	4.112 (0.995, 16.988)	0.051
Smoking history (No)	2.746 (1.296, 5.817)	0.008	9.290 (2.104, 41.028)	0.003
Drinking history (No)	1.646 (0.841, 3.223)	0.146	0.375 (0.077, 1.828)	0.225
Body mass index (Kg/m^2)	0.976 (0.875, 1.089)	0.669		
Hemoglobin (g/L)	0.979 (0.959, 0.999)	0.04	0.983 (0.954, 1.013)	0.273
White blood cell (10∧9/L)	1.030 (0.888, 1.194)	0.698		
Platelet (10∧9/L)	1.001 (0.996, 1.003)	0.826		
Aspartate transaminase (IU/L)	0.999 (0.976, 1.022)	0.93		
Alanine aminotransferase (IU/L)	1.003 (0.990, 1.017)	0.619		
Creatinine (μmol/L)	1.005 (0.996, 1.014)	0.277		
Carcinoembryonic antigen	1.001 (1.000, 1.003)	0.16	0.999 (0.997, 1.002)	0.492
Cytokeratin 19 fragments	1.071 (1.002, 1.144)	0.042	1.052 (0.958, 1.156)	0.285
Neuron-specific enolase	1.038 (0.979, 1.010)	0.208	1.007 (0.913, 1.109)	0.894
Glycated hemoglobin	0.958 (0.753, 1.219)	0.729	0.825 (0.549, 1.240)	0.355
Tumor location				
Low left	0.891 (0.327, 2.424)	0.821	1.079 (0.254, 4.585)	0.917
Upper right	1.301 (0.534, 3.167)	0.563	1.956 (0.496, 7.718)	0.338
Center right	1.583 (0.454, 5.527)	0.471	1.092 (0.165, 7.242)	0.927
Low right	1.484 (0.473, 4.656)	0.498	1.290 (0.249, 6.677)	0.762
Hilus of the lung	1.188 (0.150, 9.408)	0.871	0.861 (0.0197, 37.626)	0.938
Nodule property				
Ground glass nodules	0.857 (0.069, 10.667)	0.905	3.529 (0.113, 110.208)	473
Solid nodules	4.963 (0.539, 45.715)	0.157	9.688 (0.420, 223.419)	0.156
Diabetes treatment				
Insulin	1.942 (0.734, 5.141)	0.181	1.193 (0.235, 6.0444)	0.832
Oral hypoglycemic drugs + Insulin	1.195 (0.281, 5.078)	0.809	1.744 (0.148, 20.546)	0.658
Diet control + exercise	1.412 (0.572, 3.487)	0.454	1.007 (0.229, 4.422)	0.993
Disease interval time (years)	1.087 (0.792, 1.490)	0.606	1.215 (0.695, 2.122)	0.494
Clinical stage				
II	6.667 (1.176, 37.781)	0.032	17.798 (1.975, 160.383)	0.01
III	0.556 (0.059, 5.241)	0.608	0.989 (0.074, 13.187)	0.993
IV	9.833 (3.689, 26.215)	<0.001	16.939 (4.368, 65.692)	<0.001

OR, odds ratio; CI, confidence interval.

within exon E3 (34). This suggests a potential correlation between gene mutation and the clinical stage of lung cancer. In contrast to previous studies, our univariate and multivariate analyses revealed that clinical stage was associated with gene mutation in lung adenocarcinoma patients with diabetes, with stages II and VI showing a higher likelihood of gene mutation. The analysis may be attributed to population differences or a small sample size. Sex, smoking history, and tumor stage influence genetic mutations and are influenced by genetic and environmental factors.

Sex, smoking, tumor stage, and gene mutation (GSTGM) significantly influence the treatment outcomes and prognosis of lung adenocarcinoma patients. Female patients generally respond better to treatment and have longer survival times, likely due to healthier lifestyle choices (35). Furthermore, smokers are more likely to develop resistant genetic mutations (36) that limit treatment options and increase complications. Meanwhile, early-stage tumors are typically surgically removed, while intermediate and advanced stages require

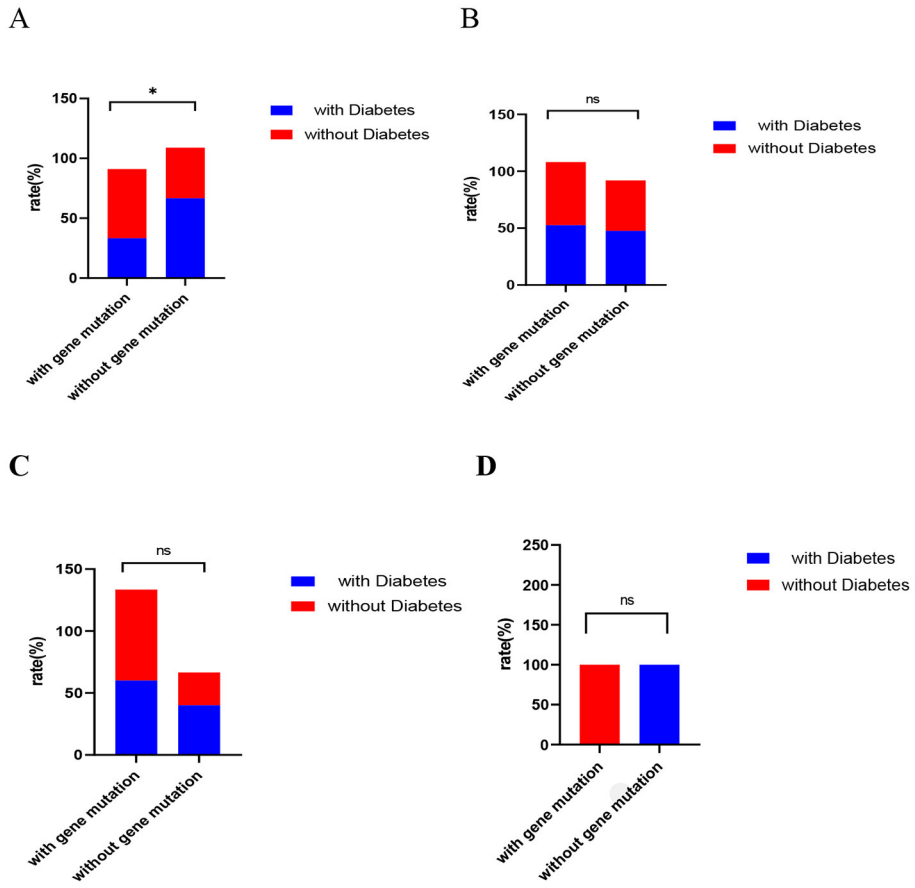

FIGURE 2
Comparison of gene mutations in ADC patients with or without diabetes in subgroup analysis. The gene mutation rate among patients with lung adenocarcinoma was found to be intermediate between those with and without diabetes [male smokers, **(A)**; male non-smokers, **(B)**; female non-smokers, **(C)**; female smokers, **(D)**]. Statistical analyses were conducted using Fisher's exact test and the Chi-Square test, with "ns" denoting $P > 0.05$, and $P < 0.05$ indicated by an asterisk ("*").

a comprehensive approach. Targeted therapies for specific genetic mutations have proven effective in improving survival rates (37, 38). Personalized treatment plans should involve a thorough assessment of the patient's overall health alongside multidisciplinary expertise for optimal management. Promoting healthy lifestyles and addressing psychological wellbeing is essential for enhancing treatment effectiveness and quality of life.

Diabetes and lung adenocarcinoma are linked through gene mutations and complex interactions. High blood sugar levels can damage enzymes and DeoxyriboNucleic Acid (DNA), potentially causing tumors, and provide energy for cancer cell growth (39, 40). Insulin resistance disrupts metabolism, alters cytokine levels, and can stimulate tumor growth while inhibiting cell death (41). Elevated insulin levels in diabetes can also enhance the effects of Insulin-like Growth Factor (IGF) and Vascular Endothelial Growth Factor (VEGF), promoting tumor cell proliferation (42). In short, diabetes may affect cell cycle, apoptosis, and DNA repair, causing mutations in related genes, contributing to the tumor's development.

The current investigation was subject to several limitations. To begin with, it was a single-center retrospective study conducted in Chongqing, China, which featured a small sample size. Secondly, the study's inclusion of mutated genes was incomplete, and it did not collect data on specific medication regimens for diabetes. Thirdly, the prognosis of all participants was not evaluated or analyzed in our research. Fourthly, there may have been a few errors in the data collection process. Fifthly, there may be other risk factors influencing genetic mutation, such as chronic obstructive pulmonary disease (COPD), tuberculosis, and Interstitial Lung Disease (ILD). Despite these limitations, the study also boasts several benefits: firstly, it is the first study to explore the relationship between diabetes and lung tumor gene mutations. Secondly, it reaffirmed the relationship between smoking history, gender, and lung cancer gene mutations.

In conclusion, patients with lung adenocarcinoma who also have diabetes may exhibit a reduced rate of gene mutation, particularly among male smokers. Gender, smoking history, and clinical stage are associated with gene mutation rates. However, the precise mechanisms of action remain to be fully understood. To achieve a deeper comprehension of this matter, additional basic research is required to elucidate the interactions between diabetes and lung adenocarcinoma and the fundamental reasons behind alterations in gene mutation rates.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation. Requests to access these datasets should be directed to 1946966229@qq.com.

Ethics statement

The studies involving humans were approved by the Second Affiliated Hospital, Chongqing Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

LY: Writing – original draft. YH: Writing – review & editing. TZ: Data curation, Writing – review & editing. HY: Writing – original draft, Writing – review & editing. DJ: Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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