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ORIGINAL RESEARCH

# Regulatory T Cell-Related Gene Polymorphisms are Associated with Risk of Lung Cancer in Patients with COPD

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**Background:** The chronic inflammatory state of COPD can lead to an imbalance in immune cell subsets, specifically manifested as an increase in regulatory T cells (Tregs), which may promote tumor immune escape. However, few studies have reported the correlation between polymorphisms of Treg-related *FOXP3, IL2*, and *TGFB1* genes and the risk of lung cancer in COPD patients.

**Methods:** Six SNPs in *FOXP3, IL2*, and *TGFB1* were genotyped in 582 patients with COPD combined with lung cancer (the study group) and 603 patients with simple COPD (the control group) using a MassARRAY platform.

**Results:** By comparing the allele frequencies of the study group and the control group, three SNPs were found to be associated with the risk of lung cancer in patients with COPD, including *FOXP3*-rs3761547, *IL2*-rs2069762 and *TGFB1*-rs4803455 ($p < 0.0001$). Genotype frequencies analysis revealed that *FOXP3*-rs3761547-TC/CC, *IL2*-rs2069762-AC/CC and *TGFB1*-rs4803455-CA/AA genotypes were associated with increased risk of lung cancer in COPD patients ($p < 0.0001$). Moreover, genetic model analysis results showed that *FOXP3*-rs3761547 had the highest risk of causing lung cancer in COPD patients in the recessive model, at 2.68 times ($p < 0.0001$). *IL2*-rs2069762 and *TGFB1*-rs4803455 had the highest pathogenic risks in the dominant model, at 2.11 and 3.27 times respectively ($p < 0.0001$). Additionally, stratified analyses showed that the three SNPs were significantly associated with the risk of lung cancer in both smoking and non-smoking COPD patients ($p < 0.0001$), and the risk of lung squamous cell carcinoma and lung adenocarcinoma in COPD patients ($p < 0.001$).

**Conclusion:** Our results suggest that Treg-related genes polymorphisms may serve as susceptibility markers for lung cancer in the COPD population.

**Keywords:** COPD, single nucleotide polymorphisms, SNPs, lung cancer, *FOXP3*, *IL2*, *TGFB1*

## Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous disorder characterized by chronic respiratory diseases caused by abnormalities in the airways and/or alveoli (pulmonary emphysema).[1] Its incidence has been gradually increasing in recent years.[2] Lung cancer is a malignant tumor that originates from the epithelial cells of the respiratory tract (bronchi, bronchioles, and alveoli), and it is one of the tumors with the highest incidence and mortality rates.[3] Previous literature reports indicate that COPD is not directly associated with lung cancer; however, the risk of lung cancer in COPD patients is higher than that in non-COPD patients, and the prevalence of lung cancer in COPD patients is 5.08%.[4] Studies have shown that 50–70% of lung cancer patients exhibit lung function impairment, with a higher probability of COPD among patients with lung squamous cell carcinoma, and the main reason is that both COPD and lung cancer share many common risk factors and pathophysiological mechanisms.[5] If the high-risk COPD patients prone to lung cancer can be identified and predicted, it will help to intervene in advance and implement targeted preventive

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measures. Moreover, in clinical practice, due to the similar clinical symptoms of some atypical or early-stage lung cancer patients and those with simple COPD, it is easy to overlook some lung cancer-related screenings, resulting in most cases being diagnosed at an advanced stage and having a poor prognosis. Therefore, finding low-cost and easily accessible predictive indicators will be of great significance for identifying high-risk groups in clinical practice.

The chronic inflammatory state of COPD can lead to an imbalance in immune cell subsets, specifically manifested as an increase in regulatory T cells (Tregs), which may promote tumor immune escape. Treg cells mainly inhibit inflammatory responses through mechanisms such as directly suppressing the activation of effector T cells, secreting anti-inflammatory cytokines such as IL-10 and TGF-β, and influencing metabolic pathways.[6,7] Studies have shown that the number of Treg cells in COPD patients is significantly increased. The proportion of Treg cells in the peripheral blood of moderate COPD patients is approximately 20% higher than that of healthy individuals, and this increase inhibits the immune response that clears lung damage, leading to the persistence of chronic inflammation.[8] Moreover, the number of Treg cells is closely related to the tumor stage and prognosis of lung cancer patients. The higher the proportion of Treg cells in advanced lung cancer patients, the lower the 5-year survival rate.[9] Accumulating evidence has elucidated the profile of Tregs in the context of COPD-related lung cancer. Unlike the immunosuppressive phenotype observed in solitary lung cancer, Tregs in comorbid patients exhibit a complex interplay. Mendelian randomization studies suggest a causal mediating role of Tregs between COPD and lung cancer.[10] Phenotypically, although the suppressive function of peripheral Tregs may be paradoxically reduced in comorbidity, there is a significant accumulation of FoxP3+ Tregs within the lung tumor microenvironment,[11] where they express high levels of immune checkpoint molecules such as PD-1 and CTLA-4.[12] Furthermore, the chronic inflammatory state of COPD drives an imbalance in the Treg/Th17 ratio, shifting the immune landscape towards a pro-tumorigenic profile.[13] Therefore, we have to pay attention to the relationship between the regulatory mechanisms related to Treg cells and the occurrence of lung cancer in COPD patients. Forkhead box protein 3 (FOXP3) is a key transcription factor that controls the development and function of Treg cells and plays a core role in maintaining immune homeostasis.[14] IL-2 is a key inducing condition for the differentiation and maturation of Treg cells, while TGF-β is a key cytokine secreted by Treg cells.[15] However, few studies have reported the correlation between polymorphisms of *FOXP3, IL2*, and *TGFB1* genes and the risk of lung cancer in COPD patients.

Based on the literature reports and the minor allele frequency of the Asian population in NCBI (> 5%), we selected six candidate SNPs located in the *FOXP3, IL2* and *TGFB1* genes. The rs3761547, rs2280883 and rs2232365 of the *FOXP3* were respectively associated with the risk of interstitial pneumonia,[16] colorectal cancer[17] and Crohn's disease.[18] *IL2*-rs2069762 was reported to be related to the risk of colorectal cancer and mantle cell lymphoma,[19,20] while the *IL2*-rs2069772 was related to the change in serum IL-2 level.[21] Additionally, the *TGFB1*-rs4803455 was associated with the poor prognosis of lung cancer patients.[22] However, little study has focused on whether these SNPs are related to the risk of lung cancer in COPD patients. In this study, we detected the polymorphisms of these SNPs in patients with simple COPD and those with COPD combined with lung cancer, and analyzed whether they were related to the risk of lung cancer in COPD patients, in order to find high-risk individuals with a predisposition to lung cancer in COPD patients and provide guidance for early prevention and targeted treatment.

# Materials and Methods

## Subjects

This study collected a total of 1185 COPD patients who visited the Department of Respiratory Medicine in Shanxi Province Cancer Hospital from January 2020 to June 2025. Among them, 582 patients were histopathologically diagnosed with COPD combined with lung cancer (the study group), and 603 patients with simple COPD were hospitalized during the same period (the control group).

Inclusion criteria: (1) all patients diagnosed with COPD met the diagnostic criteria of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria; (2) all patients diagnosed with COPD combined with lung cancer met the following conditions: they were initially diagnosed with COPD through pulmonary function tests; or they have previously been diagnosed with COPD, and were re-diagnosed as COPD through pulmonary function assessment during hospitalization. The diagnosis of lung cancer was obtained through pathological specimens obtained through electronic

bronchoscopy biopsy or percutaneous lung puncture, and subjected to pathological examination; (3) patients with simple COPD who did not have any lung tumors detected by chest CT examination; (4) patients who were admitted for the first time and whose clinical data were fully recorded.

Exclusion criteria: (1) patients who have previously undergone surgery, radiotherapy, targeted therapy, or immunotherapy; (2) those whose pathological results confirm the presence of lung cancer in addition to other tumors; (3) patients with underlying pulmonary diseases (such as tuberculosis, bronchiectasis, etc).; (4) patients with important organ functional failures such as blood system diseases, liver and kidney diseases; (5) presence of autoimmune diseases, including but not limited to multiple sclerosis and generalized vitiligo.

All participants provided written informed consent. The study was approved by the Ethics Committee of Shanxi Province Cancer Hospital (No. 2019–072) and was conducted in accordance with the World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects.

## Genotyping

All blood samples were collected upon admission, with 5 mL of venous blood being collected from each patient. DNA extraction is carried out using a PureLink™ Pro 96 Kit (Invitrogen, USA) according to the instructions provided. Genotyping is conducted based on the Sequenom Massarray platform. Assay design and mass spectrometric genotyping were performed as previously described.[23] The specific operation steps can be found in our previous research.[24]

## Statistical Analyses

The basic information and genotype data of the research subjects were summarized and organized using SPSS 20.0. The gender and smoking status between the study group and the control group were compared using the chi-square test, and the age differences were compared using the *t*-test. Based on the genotype data, the minimum allele frequency (MAF) and Hardy-Weinberg equilibrium (HWE) can be calculated. At the same time, chi-square test and logistic regression can be used to compare the differences in allele and genotype frequencies between the study group and the control group, thereby obtaining odds ratios (ORs) and 95% confidence intervals (CIs). Statistical significance was set at $p < 0.05$.

# Results

This study included 584 patients with COPD combined with lung cancer as the study group, and 603 patients with simple COPD as the control group. Table 1 shows the gender, age, GOLD stage and smoking history of the two groups of research

**Table 1** Basic Characteristics of the Subjects

| Characteristics | COPD-LC (n=584) | COPD (n=603) | $\chi^2$/t | *p* |
|---|---|---|---|---|
| Gender (%) | | | 0.271 | 0.603 |
| Male | 452 (77.4) | 459 (76.1) | | |
| Female | 132 (22.6) | 144 (23.9) | | |
| Age | | | 0.895 | 0.371 |
| Mean ±SD | 67.59±10.10 | 67.06±10.21 | | |
| Smoking (%) | | | 0.078 | 0.780 |
| Yes | 438 (75.0) | 448 (74.3) | | |
| No | 146 (25.0) | 155 (25.7) | | |
| GOLD stage (%) | | | 0.312 | 0.958 |
| 1 (mild) | 112 (19.2) | 120 (19.9) | | |
| 2 (moderate) | 276 (47.3) | 289 (47.9) | | |
| 3 (severe) | 148 (25.3) | 145 (24.1) | | |
| 4 (very severe) | 48 (8.2) | 49 (8.1) | | |
| Pathological type | | | | |
| Squamous cell carcinoma | 410 | | | |
| Adenocarcinoma | 154 | | | |
| Others | 20 | | | |


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subjects. After chi-square or *t*-test comparisons, there were no significant differences in gender, age, GOLD stage and smoking status between the two groups. In addition, the patients in the study group included different types of lung cancer, among which there were 410 cases of squamous cell carcinoma, 154 cases of adenocarcinoma, and 20 cases of other types.

Table 2 lists the basic information of six SNPs on the *FOXP3, IL2* and *TGFB1* genes, including the alleles and the MAFs in the two groups. All SNPs are in accordance with the HWE (HWE $p > 0.05$). By comparing the allele frequencies of the study group and the control group, a logistic regression model was used to determine that three SNPs might be associated with the risk of lung cancer in patients with COPD. These SNPs are *FOXP3*-rs3761547 (OR=1.955, 95% CI: 1.617–2.363, $p < 0.0001$), *IL2*-rs2069762 (OR=1.704, 95% CI: 1.443–2.012, $p < 0.0001$) and *TGFB1*-rs4803455 (OR=2.405, 95% CI: 2.036–2.840, $p < 0.0001$).

Table 3 conducts a statistical analysis on the distribution and differences of the genotype frequencies of SNPs in the study group and the control group. Taking the wild-type genotype as the reference, it calculates the relative risk ratios of heterozygous and homozygous mutant genotypes. It can be seen that for *FOXP3*-rs3761547, compared with TT genotype carriers, COPD patients carrying the TC and CC genotypes had their risk of developing lung cancer increase to 1.98 times and 3.47 times, respectively ($p < 0.0001$). For *IL2*-rs2069762, the AC and CC genotypes also showed 1.93 and 2.77 -times higher

**Table 2** The Minor Allele Frequencies of Candidate SNPs and Their Effect on the Risk of LC in Patients with COPD

| SNP | Gene | Position | Allele | MAF-COPD | MAF-COPD-LC | HWE *p* | OR (95% CI) | *p* |
|---|---|---|---|---|---|---|---|---|
| rs3761547 | *FOXP3* | chrX:49262004 | T>C | 0.19 | 0.31 | 0.29 | 1.955 (1.617–2.363) | <0.0001* |
| rs2280883 | *FOXP3* | chrX:49252667 | T>C | 0.16 | 0.18 | 0.46 | 1.130 (0.912–1.399) | 0.264 |
| rs2232365 | *FOXP3* | chrX:49259429 | T>C | 0.33 | 0.34 | 0.36 | 1.046 (0.882–1.240) | 0.608 |
| rs2069762 | *IL2* | chr4:122456825 | A>C | 0.33 | 0.46 | 0.71 | 1.704 (1.443–2.012) | <0.0001* |
| rs2069772 | *IL2* | chr4:122451978 | T>C | 0.14 | 0.16 | 0.22 | 1.212 (0.965–1.522) | 0.098 |
| rs4803455 | *TGFB1* | chr19:41345604 | C>A | 0.45 | 0.67 | 0.81 | 2.405 (2.036–2.840) | <0.0001* |

**Note**: *$p < 0.05$ indicates statistical significance.
**Abbreviations**: SNP, single nucleotide polymorphism; MAF, minor allele frequency; HWE, Hardy–Weinberg equilibrium; OR, odds ratio; CI, confidence interval.

**Table 3** The Genotype Frequencies of Candidate SNPs and Their Association with Risk of LC in Patients with COPD

| SNP | Genotype | COPD | COPD-LC | OR (95% CI) | *p* |
|---|---|---|---|---|---|
| rs3761547 | TT | 400 (66.3%) | 278 (47.6%) | 1 | <0.0001* |
| | TC | 177 (29.4%) | 245 (42%) | 1.98 (1.55–2.54) | |
| | CC | 26 (4.3%) | 61 (10.4%) | 3.47 (2.13–5.64) | |
| rs2280883 | TT | 420 (69.7%) | 392 (67.1%) | 1 | 0.5 |
| | TC | 170 (28.2%) | 174 (29.8%) | 1.07 (0.83–1.39) | |
| | CC | 13 (2.2%) | 18 (3.1%) | 1.53 (0.73–3.17) | |
| rs2232365 | TT | 274 (45.4%) | 252 (43.1%) | 1 | 0.6 |
| | TC | 257 (42.6%) | 264 (45.2%) | 1.13 (0.89–1.44) | |
| | CC | 72 (11.9%) | 68 (11.6%) | 1.02 (0.70–1.48) | |
| rs2069762 | AA | 273 (45.3%) | 164 (28.1%) | 1 | <0.0001* |
| | AC | 262 (43.5%) | 307 (52.6%) | 1.93 (1.49–2.49) | |
| | CC | 68 (11.3%) | 113 (19.4%) | 2.77 (1.94–3.96) | |
| rs2069772 | TT | 447 (74.1%) | 408 (69.9%) | 1 | 0.2 |
| | TC | 149 (24.7%) | 166 (28.4%) | 1.23 (0.95–1.59) | |
| | CC | 7 (1.2%) | 10 (1.7%) | 1.59 (0.60–4.23) | |
| rs4803455 | CC | 181 (30%) | 68 (11.6%) | 1 | <0.0001* |
| | CA | 296 (49.1%) | 253 (43.3%) | 2.28 (1.65–3.16) | |
| | AA | 126 (20.9%) | 263 (45%) | 5.59 (3.94–7.94) | |

**Note**: *$p < 0.05$ indicates statistical significance.
**Abbreviations**: SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval.

risk of disease compared to the AA genotype ($p < 0.0001$). Furthermore, the CA and AA genotypes of *TGFB1*-rs4803455 also increase the risk of lung cancer by 2.28 and 5.59 times compared to the CC genotype ($p < 0.0001$).

Table 4 introduced three classic genetic models to analyze the risk of lung cancer in COPD patients caused by SNPs, and the results were consistent with those of the allele and genotype analysis. Three SNPs, *FOXP3*-rs3761547, *IL2*-rs2069762 and *TGFB1*-rs4803455, were found to be significantly associated with the occurrence of lung cancer in COPD patients under all three models ($p \leq 0.0001$). Among them, *FOXP3*-rs3761547 had the highest risk of causing lung cancer in COPD patients in the recessive model ($p < 0.0001$), at 2.68 times. *IL2*-rs2069762 and *TGFB1*-rs4803455 had the highest pathogenic risks in the dominant model, at 2.11 and 3.27 times respectively ($p < 0.0001$).

Based on the analysis of the above alleles, genotypes and genetic models, three SNPs related to the risk of lung cancer in COPD patients were identified. We conducted stratified analyses separately in the smoking and non-smoking populations (Table 5). It can be seen that the three SNPs were significantly associated with the risk of lung cancer in both smoking and non-smoking COPD patients. In smoking COPD patients, *FOXP3*-rs3761547 and *TGFB1*-rs4803455 led to the highest lung cancer risk in the recessive model, being 2.67 times and 3.31 times higher, respectively ($p_{rs3761547} = 0.0004$, $p_{rs4803455} < 0.0001$); while *IL2*-rs2069762 led to the highest lung cancer risk in the dominant model, being 1.95 times ($p < 0.0001$). For non-smoking COPD patients, *FOXP3*-rs3761547 and *IL2*-rs2069762 caused the highest pathogenic risk in the recessive model,

**Table 4** The Association Between *FOXP3, IL2* and *TGFB1* Polymorphisms and Risk of LC in Patients with COPD

| SNP | Model | Genotype | COPD | COPD-LC | OR (95% CI) | *p* |
|---|---|---|---|---|---|---|
| rs3761547 | Dominant | TT | 400 (66.3%) | 278 (47.6%) | 1 | <0.0001* |
| | | TC-CC | 203 (33.7%) | 306 (52.4%) | 2.17 (1.72–2.74) | |
| | Recessive | TT-TC | 577 (95.7%) | 523 (89.5%) | 1 | <0.0001* |
| | | CC | 26 (4.3%) | 61 (10.4%) | 2.68 (1.66–4.31) | |
| | Log-additive | / | / | / | 1.92 (1.59–2.32) | <0.0001* |
| rs2280883 | Dominant | TT | 420 (69.7%) | 392 (67.1%) | 1 | 0.4 |
| | | TC-CC | 183 (30.4%) | 192 (32.9%) | 1.11 (0.87–1.42) | |
| | Recessive | TT-TC | 590 (97.8%) | 566 (96.9%) | 1 | 0.3 |
| | | CC | 13 (2.2%) | 18 (3.1%) | 1.50 (0.72–3.11) | |
| | Log-additive | / | / | / | 1.12 (0.90–1.40) | 0.29 |
| rs2232365 | Dominant | TT | 274 (45.4%) | 252 (43.1%) | 1 | 0.4 |
| | | TC-CC | 329 (54.6%) | 332 (56.9%) | 1.11 (0.88–1.39) | |
| | Recessive | TT-TC | 531 (88.1%) | 516 (88.4%) | 1 | 0.8 |
| | | CC | 72 (11.9%) | 68 (11.6%) | 0.96 (0.68–1.37) | |
| | Log-additive | / | / | / | 1.05 (0.88–1.24) | 0.59 |
| rs2069762 | Dominant | AA | 273 (45.3%) | 164 (28.1%) | 1 | <0.0001* |
| | | AC-CC | 330 (54.7%) | 420 (71.9%) | 2.11 (1.65–2.69) | |
| | Recessive | AA-AC | 535 (88.7%) | 471 (80.7%) | 1 | 0.0001* |
| | | CC | 68 (11.3%) | 113 (19.4%) | 1.92 (1.38–2.66) | |
| | Log-additive | / | / | / | 1.72 (1.45–2.04) | <0.0001* |
| rs2069772 | Dominant | TT | 447 (74.1%) | 408 (69.9%) | 1 | 0.1 |
| | | TC-CC | 156 (25.9%) | 176 (30.1%) | 1.24 (0.96–1.60) | |
| | Recessive | TT-TC | 596 (98.8%) | 574 (98.3%) | 1 | 0.4 |
| | | CC | 7 (1.2%) | 10 (1.7%) | 1.50 (0.57–3.99) | |
| | Log-additive | / | / | / | 1.23 (0.97–1.56) | 0.08 |
| rs4803455 | Dominant | CC | 181 (30%) | 68 (11.6%) | 1 | <0.0001* |
| | | CA-AA | 422 (70%) | 516 (88.4%) | 3.27 (2.40–4.44) | |
| | Recessive | CC-CA | 477 (79.1%) | 321 (55%) | 1 | <0.0001* |
| | | AA | 126 (20.9%) | 263 (45%) | 3.11 (2.41–4.02) | |
| | Log-additive | / | / | / | 2.38 (2.00–2.82) | <0.0001* |

**Note**: *$p < 0.05$ indicates statistical significance.
**Abbreviations**: SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval.

**Table 5** The Association Between rs3761547, rs2069762 and rs4803455 and Risk of LC in Patients with COPD in Smokers and Non-Smokers

| SNP | Model | Genotype | Smokers | | | | Non-Smokers | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | COPD | COPD-LC | OR (95% CI) | *p* | COPD | COPD-LC | OR (95% CI) | *p* |
| rs3761547 | Dominant | TT | 296 (66.1%) | 209 (47.7%) | 1 | <0.0001* | 104 (67.1%) | 69 (47.3%) | 1 | 0.0005* |
| | | TC-CC | 152 (33.9%) | 229 (52.3%) | 2.14 (1.63–2.81) | | 51 (32.9%) | 77 (52.7%) | 2.27 (1.42–3.62) | |
| | Recessive | TT-TC | 430 (96%) | 395 (90.2%) | 1 | 0.0004* | 147 (94.8%) | 128 (87.7%) | 1 | 0.022* |
| | | CC | 18 (4%) | 43 (9.8%) | 2.67 (1.51–4.73) | | 8 (5.2%) | 18 (12.3%) | 2.66 (1.11–6.35) | |
| | Log-additive | / | / | / | 1.92 (1.53–2.39) | <0.0001* | / | / | 1.93 (1.34–2.79) | 0.003* |
| rs2069762 | Dominant | AA | 198 (44.2%) | 126 (28.8%) | 1 | <0.0001* | 75 (48.4%) | 38 (26%) | 1 | 0.001* |
| | | AC-CC | 250 (55.8%) | 312 (71.2%) | 1.95 (1.48–2.58) | | 80 (51.6%) | 108 (74%) | 2.71 (1.65–4.44) | |
| | Recessive | AA-AC | 394 (88%) | 355 (81%) | 1 | 0.0038* | 141 (91%) | 116 (79.5%) | 1 | 0.0029* |
| | | CC | 54 (12.1%) | 83 (18.9%) | 1.72 (1.19–2.50) | | 14 (9%) | 30 (20.6%) | 2.76 (1.38–5.53) | |
| | Log-additive | / | / | / | 1.61 (1.32–1.96) | <0.0001* | / | / | 2.12 (1.49–3.02) | <0.0001* |
| rs4803455 | Dominant | CC | 137 (30.6%) | 52 (11.9%) | 1 | <0.0001* | 44 (28.4%) | 16 (11%) | 1 | 0.0001* |
| | | CA-AA | 311 (69.4%) | 386 (88.1%) | 3.26 (2.29–4.64) | | 111 (71.6%) | 130 (89%) | 3.33 (1.77–6.25) | |
| | Recessive | CC-CA | 360 (80.4%) | 242 (55.2%) | 1 | <0.0001* | 117 (75.5%) | 79 (54.1%) | 1 | 0.0001* |
| | | AA | 88 (19.6%) | 196 (44.8%) | 3.31 (2.45–4.47) | | 38 (24.5%) | 67 (45.9%) | 2.65 (1.62–4.33) | |
| | Log-additive | / | / | / | 2.44 (2.00–2.99) | <0.0001* | / | / | 2.22 (1.58–3.11) | <0.0001* |

**Note**: *$p < 0.05$ indicates statistical significance.

**Abbreviations**: SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval.



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being 2.66 and 2.76 times higher, respectively ($p_{rs3761547} = 0.022$, $p_{rs2069762} = 0.0029$); while *TGFB1*-rs4803455 caused the highest pathogenic risk in the dominant model, being 3.33 times ($p = 0.0001$).

Furthermore, considering the differences in the pathogenic mechanisms of different lung cancer pathological types, we conducted stratified analysis on patients with COPD combined with lung squamous cell carcinoma and lung adenocarcinoma (Table 6). It can be seen that the three SNPs were significantly associated with the risk of lung squamous cell carcinoma in COPD patients in all genetic models. Especially in the recessive model, *FOXP3*-rs3761547, *IL2*-rs2069762 and *TGFB1*-rs4803455 led to the highest risk of lung squamous cell carcinoma, which were 2.49, 2.01 and 3.07 times higher, respectively ($p_{rs3761547} = 0.0004$, $p_{rs2069762} = 0.0001$, $p_{rs4803455} < 0.0001$). While in lung adenocarcinoma, the three SNPs had the highest pathogenic risk in the dominant model, which were 3.76, 2.59 and 4.66 times higher, respectively ($p < 0.0001$).

## Discussion

The incidence and mortality rates of COPD and lung cancer remain consistently high. Both of the diseases are lung diseases and are interrelated. COPD can increase the occurrence of lung cancer through potential mechanisms such as gene mutations and chronic inflammation.[25] Moreover, most lung cancer patients are diagnosed at an advanced stage. Therefore, early detection and diagnosis of these two diseases are of utmost importance. Due to the similar early symptoms of COPD and lung cancer, they may not be given sufficient attention and thus lead to delayed treatment. Therefore, the risk factors for COPD combined with lung cancer should be deeply understood, which has significant value and significance for clinical practice. This study focused on the common clinical manifestations of the two diseases, namely the increase in Treg cells. We examined the polymorphisms of Treg-related genes and identified three SNPs associated with the risk of lung cancer in COPD patients, *FOXP3*-rs3761547, *IL2*-rs2069762 and *TGFB1*-rs4803455. These SNPs are expected to help identify COPD patients with a predisposition to lung cancer at an early stage, providing guidance for early diagnosis and prevention in clinical practice.

FOXP3 is the main molecule that confers the immunosuppressive function of Treg cells and is also the most characteristic marker.[26] Studies have found that FOXP3 is expressed differently in the cytoplasm and nucleus of cells in many diseases, such as autoimmune diseases, benign tumors, and malignant tumors.[27] Dimitrakopoulos et al[28] reported that *FOXP3* is expressed at a low level in normal bronchial epithelium and lymphocytes, while it is overexpressed in non-small cell lung cancer (NSCLC) cells and tumor-infiltrating lymphocytes. He et al[29] discovered that the *FOXP3*-rs3761548 is correlated with NSCLC. Fu et al reported that *FOXP3* expression is related to tumor TNM stage and lymph node metastasis.[30] Tao et al reported that FOXP3 alone has no prognostic value, but it has a favorable prognostic value only when combined with the count of Treg cells.[31] Li et al observed that FOXP3 is positively correlated with the expression of immunosuppressive factors TGF-β1, IL-35, and HMOX1 in lung adenocarcinoma, suggesting that FOXP3 is involved in the immune escape state of NSCLC.[32] Yang et al demonstrated that FOXP3 can act as a co-activator to promote the Wnt/β-catenin signaling pathway, induce EMT, and promote tumor growth.[33] Additionally, studies have confirmed that the expression of FOXP3 is finely regulated by lncRNA EGFR antisense RNA 1, which promotes NSCLC cancer cell dedifferentiation through stimulating the Notch1 pathway.[34] In this study, we report for the first time that the *FOXP3*-rs3761547 mutation is associated with the risk of lung cancer in COPD patients. Combined with previous studies, we speculate that rs3761547 may affect the number and function of Treg cells by influencing the expression level of *FOXP3*, thereby playing a role in the development of lung cancer in COPD patients.

IL-2 is an immunoregulatory factor secreted by Th1 cells. When it binds to its receptor IL-2R, it causes the activation, proliferation, and differentiation of T cells in the patient's body, playing an important role in various immune regulation and pro-inflammatory processes.[35] Due to the persistent inflammatory activation state of patients with COPD, the expression level of IL-2 may increase, enhancing its ability to cooperate with other cytokines to complete immune responses and promoting the secretion of inflammatory cytokines. As a key regulatory factor of the immune system, IL-2 has a dual role in tumor immunity, being able to activate the anti-tumor function of $CD8^+$ T cells and promoting Treg-mediated immune suppression.[36] Studies have shown that compared with patients with simple lung cancer, the IL-2 levels in patients with COPD combined with lung cancer are significantly higher, and TGF-β is also significantly higher.[37] In this study, two SNPs on the *IL2* gene, rs2069762 and rs2069772, were detected. It was found that rs2069762

**Table 6** The Association Between rs3761547, rs2069762 and rs4803455 and Risk of Squamous Cell Carcinoma and Adenocarcinoma in Patients with COPD

| SNP | Model | Genotype | Squamous Cell Carcinoma | | | | Adenocarcinoma | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | COPD | COPD-LC | OR (95% CI) | *p* | COPD | COPD-LC | OR (95% CI) | *p* |
| rs3761547 | Dominant | TT | 400 (66.3%) | 215 (52.4%) | 1 | <0.0001* | 400 (66.3%) | 53 (34.4%) | 1 | <0.0001* |
| | | TC-CC | 203 (33.7%) | 195 (47.6%) | 1.79 (1.38–2.32) | | 203 (33.7%) | 101 (65.6%) | 3.76 (2.59–5.47) | |
| | Recessive | TT-TC | 577 (95.7%) | 370 (90.2%) | 1 | 0.0004* | 577 (95.7%) | 134 (87%) | 1 | 0.0002* |
| | | CC | 26 (4.3%) | 40 (9.8%) | 2.49 (1.49–4.16) | | 26 (4.3%) | 20 (13%) | 3.41 (1.84–6.30) | |
| | Log-additive | / | / | / | 1.67 (1.36–2.06) | <0.0001* | / | / | 2.77 (2.09–3.68) | <0.0001* |
| rs2069762 | Dominant | AA | 273 (45.3%) | 125 (30.5%) | 1 | <0.0001* | 273 (45.3%) | 37 (24%) | 1 | <0.0001* |
| | | AC-CC | 330 (54.7%) | 285 (69.5%) | 1.88 (1.44–2.45) | | 330 (54.7%) | 117 (76%) | 2.59 (1.73–3.88) | |
| | Recessive | AA-AC | 535 (88.7%) | 327 (79.8%) | 1 | 0.0001* | 535 (88.7%) | 130 (84.4%) | 1 | 0.1 |
| | | CC | 68 (11.3%) | 83 (20.2%) | 2.01 (1.42–2.86) | | 68 (11.3%) | 24 (15.6%) | 1.51 (0.91–2.51) | |
| | Log-additive | / | / | / | 1.64 (1.36–1.97) | <0.0001* | / | / | 1.76 (1.35–2.29) | <0.0001* |
| rs4803455 | Dominant | CC | 181 (30%) | 53 (12.9%) | 1 | <0.0001* | 181 (30%) | 13 (8.4%) | 1 | <0.0001* |
| | | CA-AA | 422 (70%) | 357 (87.1%) | 2.90 (2.07–4.06) | | 422 (70%) | 141 (91.6%) | 4.66 (2.57–8.44) | |
| | Recessive | CC-CA | 477 (79.1%) | 227 (55.4%) | 1 | <0.0001* | 477 (79.1%) | 82 (53.2%) | 1 | <0.0001* |
| | | AA | 126 (20.9%) | 183 (44.6%) | 3.07 (2.32–4.04) | | 126 (20.9%) | 72 (46.8%) | 3.37 (2.32–4.90) | |
| | Log-additive | / | / | / | 2.27 (1.88–2.74) | <0.0001* | / | / | 2.72 (2.06–3.59) | <0.0001* |

**Note**: *$p < 0.05$ indicates statistical significance.

**Abbreviations**: SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval.



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is associated with the risk of lung cancer in COPD patients, while rs2069772 has no significant correlation with the risk of the disease. Based on previous studies, we speculate that *IL2*-rs2069762 may promote Treg-mediated immune suppression by affecting the level of IL-2, thereby promoting the occurrence and development of lung cancer. However, given the "double-edged sword" role of IL-2 in tumors, this speculation and the specific mechanism still need further research.

TGF-β1 is one of the most important profibrotic cytokines, regulating cell growth and extracellular matrix deposition through autocrine or paracrine mechanisms. It can prompt fibroblasts to migrate to the damaged area, proliferate and transform into myofibroblasts, generating extracellular matrix, and forming fibrotic foci. In COPD, the increase in Treg cells can lead to elevated TGF-β1 levels, and the TGF-β1/Smads signaling transduction pathway is an important mechanism for the occurrence and development of airway remodeling in COPD.[38] However, the relationship between TGF-β1 and Treg cells is bidirectional. Under the chronic inflammatory conditions of COPD, elevated TGF-β1 from injured epithelium and activated fibroblasts may promote the conversion of naïve CD4+ T cells into FoxP3+ inducible Tregs, creating a positive feedback loop.[39] Furthermore, TGF-β1 can modulate the functional phenotype of Tregs in a context-dependent manner.[39–41] Thus, the role of TGF-β1 in Treg cells extends beyond a simple secreted product to a critical regulator of Treg quantity, function, and phenotype. Studies have shown that TGF-β1 is significantly expressed on the airway walls of COPD patients,[42] and the level of TGF-β1 is also significantly increased in NSCLC patients, suggesting that TGF-β1 plays an important role in the co-morbidity mechanism of COPD and lung cancer. Previous studies have also reported the correlation between *TGFB1* polymorphisms and the risk of COPD and lung cancer, including rs1800469 related to lung cancer[43] and rs1982073 related to COPD.[44] However, this correlation may vary among different populations or disease stages.[45] Previous studies have indicated that *TGFB1*-rs4803455 may be related to the poor prognosis of NSCLC,[22] and this study found that rs4803455 is significantly associated with the risk of lung cancer in COPD patients, suggesting that the rs4803455 mutation may participate in the regulation of TGF-β1 expression, affect the level of TGF-β1, and thereby influence the pathogenic process of lung cancer in COPD patients. However, this speculation needs to be verified in more diverse populations and larger samples.

Smoking is a common risk factor for both COPD and lung cancer. Although there was no significant difference in smoking history between the two groups of patients with simple COPD and those with COPD combined with lung cancer in this study, we still conducted stratified analyses of smokers and non-smokers. The results showed that three significant SNPs, *FOXP3*-rs3761547, *IL2*-rs2069762 and *TGFB1*-rs4803455, were all associated with the risk of lung cancer in COPD patients under various genetic models, suggesting that the promotion effect of these three SNPs on the occurrence of lung cancer in COPD patients does not rely on smoking. Moreover, in this study, there were more patients with lung squamous cell carcinoma than those with lung adenocarcinoma. We conducted stratified analyses of the two pathological types, and the results still showed that the three SNPs were significantly associated with the risks of lung adenocarcinoma and lung squamous cell carcinoma, suggesting that the polymorphisms of Treg-related genes may play a role in the pathogenesis of lung cancer of different pathological types.

Although this study identified three potential SNPs that could be used to identify individuals at risk of lung cancer among COPD patients, there are still some inevitable limitations that need to be clarified. Firstly, the research subjects of this study were was recruited from Shanxi Province Cancer Hospital and mainly from Taiyuan City and its surrounding areas in Shanxi Province. Selection bias is possible, and the genetic background of this population may not fully represent the diversity of the broader Chinese population. Therefore, our conclusions should be considered hypothesis-generating, and future population-based prospective studies are needed to confirm the generalizability of our findings. Secondly, this study employed a cross-sectional case-control design, which has inherent limitations in establishing causality or assessing predictive validity. The observed associations between Treg-related gene polymorphisms and lung cancer risk in COPD patients are correlational by nature. We cannot rule out the possibility of reverse causation (eg., lung cancer-related immune dysregulation affecting Treg profiles) or residual confounding. Thirdly, without a lung cancer-alone group, we cannot determine whether the observed associations are specific to the COPD context or represent general lung cancer risk factors that are independent of COPD status. Future studies that include all three groups (COPD alone, lung cancer alone, and comorbid group) are needed to clarify this distinction. Lastly, the biological significance of the identified SNPs remains to be elucidated. Functional experiments (including gene expression, protein

function, and Treg activity assays) are required to elucidate the biological mechanisms by which these polymorphisms may contribute to the pathogenesis of COPD-related lung cancer.

## Conclusion

In conclusion, this study compared the differences between patients with simple COPD and those with COPD combined with lung cancer, and identified three Treg-related gene polymorphisms, *FOXP3*-rs3761547, *IL2*-rs2069762 and *TGFB1*-rs4803455, which might be associated with the risk of lung cancer in COPD patients. These findings suggest that Treg-related genetic variants may serve as susceptibility markers for lung cancer in the COPD population. Future functional studies are needed to elucidate whether and how these polymorphisms directly contribute to the pathogenic process. Nevertheless, these variants may have potential for risk stratification and early prevention strategy development for COPD patients at higher risk of lung cancer.

## Data Sharing Statement

The data used in this study are available from the corresponding author upon reasonable request.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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