Correlation Analysis of the TP53 Mutation With Clinical Characteristics in the Prognosis of Non–Small Cell Lung Cancer

Clinical Medicine Insights: Oncology
Volume 17: 1–7

DOI: 10.1177/11795549231184918

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ABSTRACT

BACKGROUND: Non–small cell lung cancer (NSCLC) with *TP53* mutations has a worse prognosis. It was generally more resistant to chemotherapy and radiation. Our aim was to investigate the correlation between the *TP53* co-mutated gene and clinical features, and prognostic value in patients with NSCLC.

METHODS: Seventy-three patients with a diagnosis of NSCLC at our hospital were recruited. They were divided into the *TP53* mutation status (minor) (*TP53* MU) and *TP53* wild-type (major) (*TP53* WT) groups according to their clinical characteristics after their mutation data and clinical information were collected. Serum markers were compared between groups using Mann-Whitney *U* test. Other clinical factors were compared between groups using $\chi 2$ test and Fisher exact test. The log-rank test was used to compare survival curves.

RESULTS: Of the 73 patients with NSCLC, 37 (50.68%) were found to carry *TP53* mutation. *TP53* MU and *TP53* WT groups (n = 36) showed a significant difference in the number of smokers, incidence of squamous cell carcinoma, *EGFR* mutation, and number of advanced patients ($P < .05$), while gender, age, lymph node metastasis, and *KRAS* mutation did not differ significantly between the 2 groups. The survival curves in the *TP53/KRAS* and the *TP53/EGFR* co-mutation groups suggest that patients with NSCLC may have a shorter progression-free survival (PFS) if they carry one of the 2 types of co-mutation.

CONCLUSIONS: *TP53* gene mutations are more common in patients with NSCLC and squamous cell carcinoma. New predictive markers for NSCLC prognosis may be *TP53/KRAS* and *TP53/EGFR* co-mutations.

KEYWORDS: *TP53*, mutation rate, non–small cell lung cancer, human characteristics, correlation analysis

RECEIVED: December 13, 2022. **ACCEPTED:** June 12, 2023.

TYPE: Original Research Article

FUNDING: .The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study is funded by the Guiding Project of Fujian Provincial Department of Science and Technology (2022Y0054).

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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Introduction

Lung cancer is now the most common malignant tumour with an annual increase in mortality, and 80% to 85% of lung cancer deaths are due to non–small cell lung cancer (NSCLC).[1] Most of the patients with NSCLC are diagnosed at an advanced stage, despite major advances in screening and treatment over the past decade.[2] Non–small cell lung cancer is associated with somatic gene mutations. Targeted therapies based on individual molecular subtypes have shown to be effective. *TP53* is the most commonly mutated gene. It is also a driver gene that plays an important role in the pathogenesis of NSCLC.[3] Studies have shown that about 50% of NSCLC incidence is related to the loss of resistance to *TP53* mutations.[4] Overexpression of mutant *p53* with reduced or abolished function is often associated with resistance to conventional treatments such as cisplatin, anthracyclines (doxorubicin), alkylating agents (temozolomide), anti-oestrogens (tamoxifen), antimetabolites (gemcitabine) and *EGFR* inhibitors (cetuximab).[5] Mutations in the *TP53* gene are often associated with changes in the structure of the *p53* protein.[6] In addition, different clinical symptoms and therapeutic outcomes may be associated with *TP53* mutations. *TP53* has been shown to have prognostic significance in NSCLC in a number of studies.[7-10] However, the prognostic value and the association between the *TP53* co-mutant gene and clinical features are still unclear.

This is a retrospective study of 73 patients diagnosed with NSCLC at our hospital. The aim of the study was to evaluate the potential association between *TP53* co-mutation and clinical features that may help predict prognosis and guide further individualised treatment.

Materials and Methods

Object of study

From January 2017 to June 2021, 73 patients diagnosed with NSCLC at our hospital were recruited. Patient electronic medical record information was used for selection. The 2020 TNM/NSCLC staging standard was used to classify patients. The

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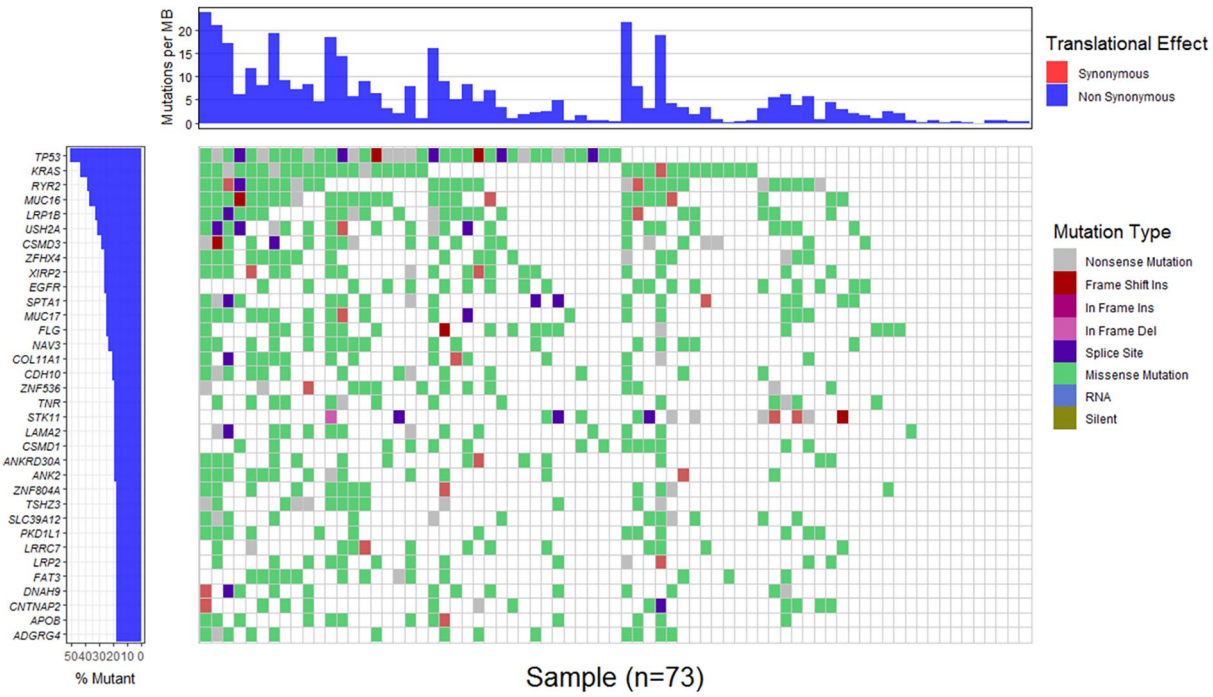

Figure 1. Waterfall map of top 15 genes detected in 73 patients with non–small cell lung cancer.
The annotation types were shown on the rights with various colours.

inclusion criteria for all patients in the current study were complete tumour markers, chest and abdomen computed tomography (CT), head and neck CT, and pathology results where available. Exclusion criteria were (1) having received antitumour treatment prior to the CT scan, (2) CT showed inflammatory lung cancer, multiple primary tumours or tumour boundaries that could not be determined, and (3) the time interval between the chest CT scan and pathological confirmation was more than 1 month.

Clinical characteristics and gene mutation detection

We retrospectively collected the basic information on all patients with NSCLC who met the research requirements. This included gender, age, pathological type, smoking history, clinical stage, medications (the anticancer drug used is afatinib) and lymph node metastasis. Serum samples were collected. Carcinoembryonic antigen (CEA), neuron-specific enolase (NSE), and cytokeratin 19 (Cyfra2-11) were measured. The study was approved by the Ethics Committee of Fujian Provincial Hospital (K2021-12-009). Informed consent was obtained from all patients. Pathological tissue samples have been obtained for genetic testing by surgical procedures, by percutaneous puncture of the lung or by bronchoscopic biopsy. Shanghai Life Gene Biotechnology Co., Ltd. performs next-generation sequencing.

Statistical methods

SPSS Statistics for Windows, version 23.0, was used for statistical analyses. Categorical variables were compared using the χ^2 and Fisher exact tests. The comparison of serum tumour indices between *TP53* MU and *TP53* WT was performed using the Mann-Whitney *U* test. The analysis software is R (https://www.R-project.org/). The waterfall map was drawn using the R package GenVisR, and the heat map was drawn using the R package ggplot2, the R package tidyverse, the R package reshape2 and the R package RColorBrewer. Progression-free survival (PFS) was examined using the Kaplan-Meier method. Differences in distributions were compared using the log-rank test. The R survminer package, the R survival package and the ggplot2 package were used to plot Kaplan-Meier survival curves. All *P* values were 2-tailed ($P < .05$).

Results

TP53 mutation in patients with NSCLC

For 73 patients with NSCLC, complete single nucleotide variant sequencing data were obtained. The proportion of patients with NSCLC with *TP53* gene mutations ranked first among all types of gene mutations (50.68%). This was followed by patients with *KRAS* (43.84%) and *RYR2* (36.99%) mutations (Figure 1). The landscape of mutation profiles was then visualised using the GenVisR package. The top 15% genes detected in 73 patients with NSCLC are shown in Figure 1. In the 73 samples, the waterfall plot showed that nonsynonymous mutation was the most common mutation effect, missense mutation was one of the most common mutation types in the altered genes. Thirty-seven patients with NSCLC with *TP53* gene mutations are shown in Figure 2. The distribution of *TP53* mutation sites across amino acids is shown. Seven novel genetic polymorphism sites were found in 37 *TP53* mutation samples.

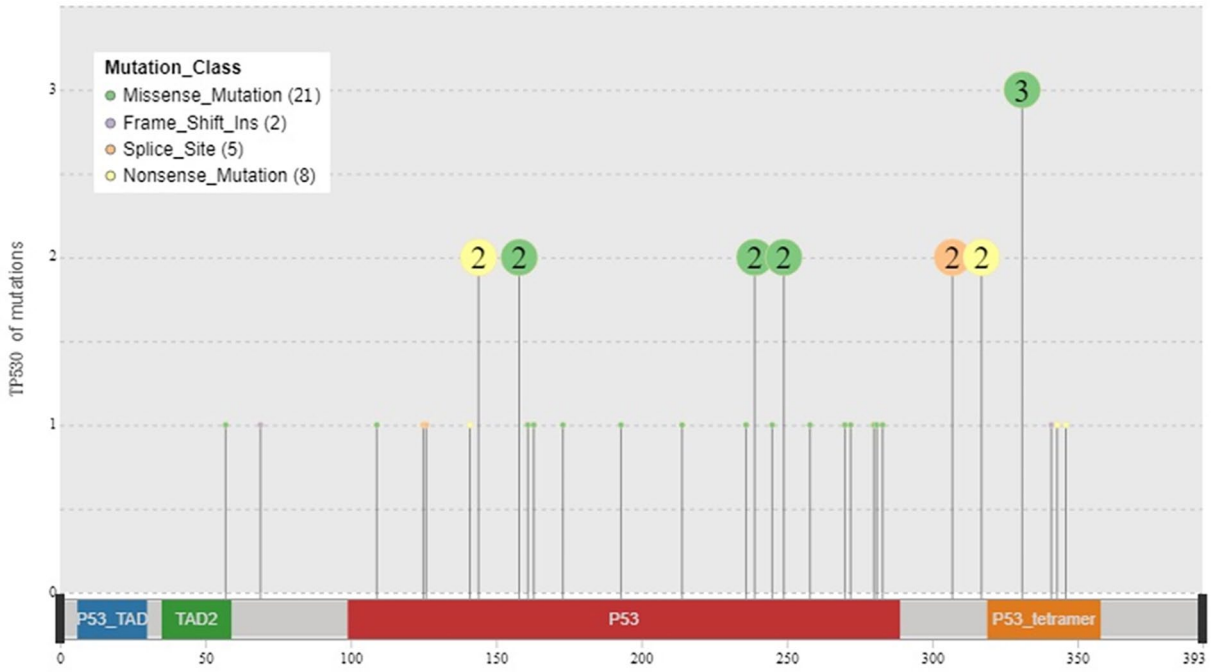

Figure 2. Distribution of *TP53* mutation sites on amino acids.

Twenty-eight genetic polymorphism sites were reported (Table 1).

The correlation between TP53 mutation and clinical characteristics

The correlation between the *TP53* mutation status and some clinical characteristics (Table 2) showed that the mutation status of *TP53* was significantly different in the tumour type, in the smoking status and in the tumour stage ($P < .05$). In addition, the *TP53* mutation status was also associated with the *EGFR* mutation status ($P < .05$). There was no significant association between the mutation status of the *TP53* gene and gender, age, lymph node metastasis or *KRAS* mutations.

The Mann-Whitney *U* test was performed for serum tumour markers (*CEA*, *NSE* and *CYFRA21*) between *TP53* MU and *TP53* WT. However, no statistically significant difference in serum tumour markers was found between the two groups (Table 3).

Prognostic analysis TP53 and its co-mutant genes

Median PFS in the *TP53* WT and *TP53* MU groups was 12.9 months (95% CI = 10.5-15.4) and 8.9 months (95% CI = 7.7-14.0), respectively. It was significantly reduced in the *TP53*/*KRAS* combo group (8.0 months, 95% CI = 4.4-12.8, $P = .0037$, compared to the other two groups) (Figure 3). Median PFS was 8.9 months (95% CI = 7.7-13.8) for patients with *TP53* mutation alone, 12.9 months (95% CI = 10.5-15.4) for patients with *TP53* wild-type and 7.9 months (95%CI = 4.6-13.0) for patients with *TP53*/*EGFR* combo mutations (Figure 4). Statistically significant differences ($P = .011$) were observed between patients with *TP53* mutation alone, *TP53* wild-type and *TP53*/*EGFR* co-mutations.

Discussion

The tumour suppressor gene *TP53* is located on the short arm of chromosome 17. It is currently one of the most widely studied tumour-related genes.[11] *TP53* gene mutation has been shown to be a driver of tumour cell proliferation, migration and invasion, a driver of tumour cell drug resistance, a driver of tumour cell disruption of normal tissue physiology and a driver of tumour cell metabolism.[12,13] The *TP53* mutation rate in NSCLC varied between studies: 50.68% in our study, 30.9% in Canale's study[14] and 56.1% in Jiao's study.[8] Tissue type, storage time and gene sequencing technology may contribute to these differences. Studies have shown that the *TP53* mutation rate in squamous cell carcinoma of the lung is significantly higher than that in adenocarcinoma of the lung.[15] TP53 mutations are closely associated with smoking status. Patients with NSCLC with a history of smoking have higher *TP53* mutation rates.[16] Differences in patient smoking status may therefore explain the difference in mutation rates between the 3 studies. In addition, wild-type mutations may be detected due to the long storage time of paraffin samples and difficult gene extraction and amplification procedures.

This study demonstrated the predictive value of *TP53*. Several studies have also suggested that *TP53* mutation is a negative prognostic factor.[8,17-23] It is associated with poor survival in patients with NSCLC who have undergone immunotherapy.[24] Jiao's research showed that the incidence of *TP53* mutation was higher in patients with mutated *EGFR* genes than in those with wild-type *EGFR* genes. However, patients, especially advanced patients with NSCLC with wild-type

Table 1. Missense mutations of TP53 identified in patients with non–small cell lung cancer.

VARIANT CLASSIFICATION	TRANSCRIPT	GDNA	AMINO ACID	REPORTED/NOVEL
Missense mutations	NM_000546.5	c.169G>A	p.D57N	Novel
Missense mutations	NM_000546.5	c.326T>G	p.F109C	rs1064796722
Missense mutations	NM_000546.5	c.473G>T	p.R158L	Novel
Missense mutations	NM_000546.5	c.473G>T	p.R158L	Novel
Missense mutations	NM_000546.5	c.482C>A	p.A161D	rs1064795691
Missense mutations	NM_000546.5	c.487T>C	p.Y163H	rs786203436
Missense mutations	NM_000546.5	c.517G>T	p.V173L	rs876660754
Missense mutations	NM_000546.5	c.578A>T	p.H193L	rs786201838
Missense mutations	NM_000546.5	c.641A>G	p.H214R	rs1057519992
Missense mutations	NM_000546.5	c.707A>G	p.Y236C	rs730882026
Missense mutations	NM_000546.5	c.716A>G	p.N239S	rs1057519999
Missense mutations	NM_000546.5	c.715A>G	p.N239D	rs876660807
Missense mutations	NM_000546.5	c.733G>T	p.G245C	rs28934575
Missense mutations	NM_000546.5	c.747G>T	p.R249S	rs28934571
Missense mutations	NM_000546.5	c.746G>T	p.R249M	rs587782329
Missense mutations	NM_000546.5	c.808T>G	p.F270V	rs1057519988
Missense mutations	NM_000546.5	c.815T>G	p.V272G	rs876660333
Missense mutations	NM_000546.5	c.838A>G	p.R280G	rs753660142
Missense mutations	NM_000546.5	c.842A>T	p.D281V	rs587781525
Missense mutations	NM_000546.5	c.848G>C	p.R283P	rs371409680
Missense mutations	NM_000546.5	c.993G>T	p.Q331H	rs11575996
Nonsense mutation	NM_000546.5	c.991C>T	p.Q331*	novel
Nonsense mutation	NM_000546.5	c.430C>T	p.Q144*	rs757274881
Nonsense mutation	NM_000546.5	c.423C>A	p.C141*	rs1057519977
Nonsense mutation	NM_000546.5	c.493C>T	p.Q165*	rs730882001
Nonsense mutation	NM_000546.5	c.949C>T	p.Q317*	rs764735889
Nonsense mutation	NM_000546.5	c.949C>T	p.Q317*	rs764735889
Nonsense mutation	NM_000546.5	c.1027G>T	p.E343*	Novel
Nonsense mutation	NM_000546.5	c.430C>T	p.Q144*	rs757274881
Nonsense mutation	NM_000546.5	c.1036G>T	p.E346*	rs1567542019
Splice site	NM_000546.5	c.919 + 1G>T	p.X307_splice	rs1131691039
Splice site	NM_000546.5	c.376-2A>G	p.X126_splice	rs786202799
Splice site	NM_000546.5	c.993 + 1G>T	p.X331_splice	rs11575997
Splice site	NM_000546.5	c.920-2A>G	p.X307_splice	rs397516439
Splice site	NM_000546.5	c.375 + 1G>T	p.X125_splice	rs1567555445
Frame shift ins.	NM_000546.5	c.1020_1021insGAAG	p.F341Efs*7	Novel
Frame shift ins.	NM_000546.5	c.205dupG	p.A69Gfs*80	Novel

Table 2. Comparative analysis of clinical characteristics between TP53 mutation patients and TP53 wild-type patients.

CLINICAL CHARACTERISTICS	TP53 MU (N = 37)	TP53 WT (N = 36)	χ^2	*P* VALUE
Gender			1.217	.270
Male	23	28		
Female	14	8		
Age			0.030	.862
<60	19	15		
⩾60	18	21		
Type			5.790	.034
Squamous cell carcinoma	31	23		
Adenocarcinoma	6	13		
Smoking			6.423	.023
Yes	32	19		
No	5	17		
Stage			7.088	.027
Stage II	6	1		
Stage III	11	4		
Stage IV	20	31		
Lymph node metastasis			1.488	.222
Yes	21	26		
No	16	10		
KRAS mutation			1.033	.309
Yes	20	12		
No	17	24		
EGFR mutation			1.216	.040
Yes	10	9		
No	27	27		

Abbreviations: TP53MU, TP53 mutation group; TP53WT, TP53 wild-type group.
$P < .05$ indicates that there is a statistical difference; $P > .05$ indicates that the difference is not significant.

Table 3. Comparison of serum tumour markers in patients with TP53 mutation and TP53 wild-type patients.

TUMOUR MARKERS	TP53 MU	TP53 WT	*Z* VALUE	*P*-VALUE
CEA	21.34 (4.05-47.23)	14.07 (4.24-74.98)	307	.369
NSE	19.78 (12.38-23.23)	18.53 (11.19-24.84)	357	.642
CYFRA21	5.08 (3.45-14.02)	5.72 (2.34-8.11)	335	.501

Abbreviations: CEA, carcinoembryonic antigen; CYFRA21, cytokeratin 19; NSE, neuron-specific enolase; TP53 MU, TP53 mutation group; TP53 WT, TP53 wild-type group.
All values are represented by M (P25-P75).
$P < .05$ indicates that there is a statistical difference; $P > .05$ indicates that the difference is not significant.

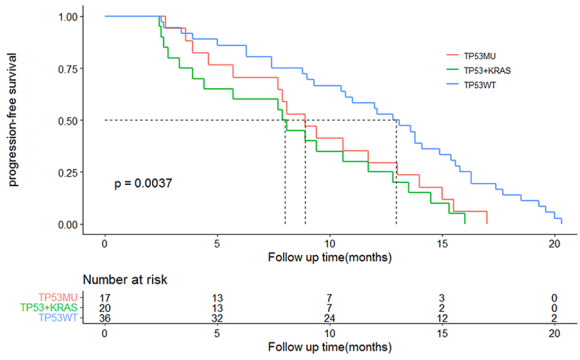

Figure 3. Survival analysis of *TP53*/*KRAS* co-mutation. TP53 MU indicates TP53 mutation group; TP53WT, TP53 wild-type group.

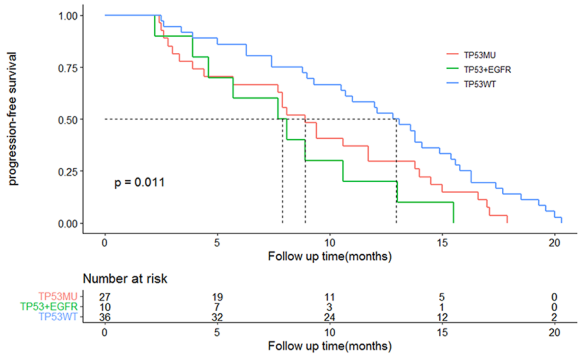

Figure 4. Survival analysis of *TP53*/*EGFR* co-mutation. TP53MU indicates TP53 mutation group; TP53WT, TP53 wild-type group.

EGFR genes, had the best prognosis if they had wild-type *TP53* genes.[8,25] In patients with *TP53*-mut/*STK11*-*EGFR*-WT malignancies, Biton et al[17] also suggested that anti-PD-1 therapy prolonged PFS. Significantly greater therapeutic benefit could be seen in patients with high PD-L1 expression than in those without.[19]

Prognostic value has also been shown for the *TP53/KRAS* co-mutation.[26] In Scheffler's study, different patterns of co-mutations were found in different *KRAS* mutant classes, and 39.4% of patients were found to have a *TP53*/*KRAS* co-mutation.[27] In patients with NSCLC, both *KRAS* and *TP53* are associated with distant metastases and poor prognosis. Mutated *KRAS*, mutated *TP53* and co-mutated *KRAS*/*TP53* all have a longer PFS period than their wild-type counterparts. Relevant studies have shown that patient survival is associated with changes in mutation burden, and that tumour heterogeneity and the development of drug resistance during treatment will affect patient PFS. Tumour drug resistance may be stronger in the *TP53* MU group, resulting in shorter patient PFS.[28] Patients with co-mutations in *PIK3CA*/*TP53* or *KRAS*/*TP53* had a shorter PFS than patients with either a *KRAS* mutation or a *TP53* mutation.[22] The mutational status of *TP53* significantly affects the clinical characteristics of patients with NSCLC. Given the short PFS in the TP53 MU group, the selection of drugs with low resistance is important for the treatment of patients. In this study, *TP53* was not significantly associated with lymph node metastasis. However, Chow's study showed the opposite.[29] Variability in the type (contains only part of the lesion, or a small amount of paracancerous tissue), quantity and quality of the pathological tissues in the samples may account for the differences in the results of the studies.

TP53 mutations are most common in patients with lung cancer who smoke. The type and extent of the mutations are related to the patient smoking status.[30,31] Our research has also confirmed that smokers are more likely to have *TP53* mutations than nonsmokers. In addition, the *TP53* mutation is associated with the pathological type. In our analysis, squamous cell carcinoma had a significantly higher *TP53* mutation rate than adenocarcinoma. This finding is consistent with Mogi's study, which reported a higher *TP53* mutation rate in squamous cell carcinoma than in adenocarcinoma.[31] The limitation of this study is the relatively small sample size. Further research on a larger population is needed.

Conclusions

A large body of data has shown that the mutation or expression of various genes in tumours can be a guide to cancer treatment. There is still debate about the relationship between *TP53* mutation status and clinical features in patients with NSCLC. Although the sample size in this study is small, it could potentially help to inform how to detect and assess NSCLC in the future clinical setting. It is hoped that *TP53* gene mutations and novel therapies targeting *TP53* in NSCLC will be investigated in subsequent clinical trials with larger sample sizes. *TP53* gene mutations are more common in patients with NSCLC and squamous cell carcinoma. New predictive markers for NSCLC prognosis may be *TP53*/*KRAS* and *TP53*/*EGFR* co-mutations.

Author Contributions

Lihuan Zhu: Proposal and design of research topics, complete the drawing of heat map, waterfall map and survival curve.
Dongsheng Zhou: Implementation of research processes, acquisition, provision and analysis of medical record information.
Yiyong Chen: Case selection.
Tianxing Guo: Thesis drafting.
Wenshu Chen: Supervise the execution of the study.
Xiaojie Pan: Provide financial support for the project, coordinate and manage the implementation of the project, and evaluate and revise the first draft of the article.

Ethical Approval

This study was approved by the Ethics Committee of Fujian Provincial Hospital (K2021-12-009) on December 8, 2021.

Data Availability Statement

The datasets used or analysed during the current study are available from the corresponding author on reasonable request.

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