Genomic landscape and prognosis of patients with *TP53*-mutated non-small cell lung cancer

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Background: The *TP53* tumor suppressor gene plays an important role in preventing and inhibiting the growth of tumor by regulating cell cycle, apoptosis and DNA repair. Meanwhile, the *TP53* gene is one of the most frequently altered gene in non-small cell lung cancer (NSCLC) patients. Mutant *TP53* (*TP53*-MUT) may lose tumor suppressor activity and gain tumor promoting functions, which play an important role in cancer risk, therapy resistance and poor prognosis. The impact of *TP53*-MUT on the prognosis of NSCLC patients need to be further studied.

Methods: We obtained genomic and clinical data from The Cancer Genome Atlas (TCGA). Mutation profiles, the TMB, disease-free survival (DFS), and overall survival (OS) were compared between patients with different *TP53*-MUT statuses.

Results: *TP53*-MUTs were detected in 46.6% of patients with lung adenocarcinoma (LUAD) (264 of 566) and 82.3% of those with lung squamous cell carcinoma (LUSC) (401 of 487). The most frequently co-mutated genes in patients with LUAD carrying a *TP53*-MUT included classic driver genes such as epidermal growth factor receptor (*EGFR*) and anaplastic large-cell lymphoma kinase (*ALK*), while Kirsten rat sarcoma viral oncogene (*KRAS*) mutations and *TP53*-MUTs appear to be mutually exclusive. This mutual exclusivity was not observed in patients with LUSC, in whom titin (*TTN*) and CUB and Sushi multiple domains 3 (*CSMD3*) were the most frequently co-mutated genes. A higher TMB was significantly associated with *TP53*-MUTs in patients with LUAD but not in those with LUSC. In patients with stage I-III NSCLC who had undergone surgery, there was no significant difference in DFS between patients carrying *TP53*-wildtype (*TP53*-WT) and *TP53*-MUTs, irrespective of histology or mutation type. However, the presence of *TP53*-MUT was associated with shorter OS in patients with LUAD (49 *vs.* 54 months, respectively; P=0.13) and significantly longer OS in those with LUSC (62 *vs.* 29 months, respectively; P=0.015).

Conclusions: In contrast to most previous studies, we revealed *TP53*-MUT characteristic in NSCLC patients according to histology-specific differences and the association between *TP53*-MUT and the mutation landscape, the TMB, and the OS. These findings suggest a need for individualized management for patients with LUAD and LUSC who carry a *TP53*-MUT, and warrant further research.

Keywords: Non-small cell lung cancer (NSCLC); lung squamous cell carcinoma (LUSC); lung adenocarcinoma (LUAD); *TP53* mutation; prognosis

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Introduction

Lung cancer is a malignant tumor with the highest morbidity and mortality worldwide (1). In 2020, there were 2.2 million new cases and 1.8 million deaths related to lung cancer (1). Lung cancer is the top-ranking malignancy in incidence and mortality in China (2). Non-small cell lung cancer (NSCLC) is the most common subtype, accounting for 83% of all lung cancer cases (3). Identification of oncogenic driver alterations in recent decades has accelerated the development of targeted therapy for NSCLC. Clinically actionable driver alterations are frequently observed in protein kinase-encoding genes such as epidermal growth factor receptor (*EGFR*) and anaplastic lymphoma kinase (*ALK*). In addition, drugs are being actively developed to target other drivers, such as Kirsten rat sarcoma viral oncogene (*KRAS*) and phosphatidylinositol 3-kinase catalytic subunit α (*PIK3CA*).

In addition to proto-oncogene activation, aberrant tumor suppressors constitute a significant type of oncogenic alterations, the most frequent of which is tumor protein 53 (*TP53*). *TP53* is located on chromosome 17p and encodes p53 (4,5). A mutant p53 loses its normal grip on the regulation of cell growth, apoptosis, and DNA repair, thereby promoting tumor initiation and growth (5). Almost 80% of *TP53* mutations (*TP53*-MUTs) are missense mutations, the rest including frameshifts, truncations, and deletions (5).

TP53-MUTs are more likely occurred in smoking NSCLC patients (6). Previous research suggests that different classes of *TP53*-MUTs, based on type and location, may have different prognostic significance (7-10). However, evidence is still accumulating regarding the association between *TP53*-MUTs and clinical features, co-mutations, and prognosis in NSCLC. Moreover, most studies have investigated NSCLC patients as a homogeneous population or focused mainly on lung adenocarcinoma (LUAD), leaving lung squamous cell carcinoma (LUSC) as an under-characterized subtype. To determine the prognostic relevance of *TP53*-MUTs in patients with LUAD and LUSC, we retrospectively analyzed data from The Cancer Genome Atlas (TCGA) database and identified differences in the mutational landscape, tumor mutation burden (TMB), disease-free survival (DFS), and overall survival (OS).

We present the following article in accordance with the REMARK reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-412/rc).

Methods

Data and patients

Genomic and clinical data for patients with NSCLC were obtained from TCGA, a publicly available database at http://www.cbioportal.org. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study cohort consisted of 1,053 patients, including 566 patients with LUAD and 487 with LUSC. Only the 931 patients with stage I–III NSCLC who underwent surgery were included for subsequent survival analyses, including 470 patients with LUAD and 461 with LUSC. OS was defined as the time interval between the date of tumor biopsy and the date of death. DFS was defined as the time from the day of surgery to disease progression or the last follow-up.

Four different binary systems were used to classify *TP53*-MUTs. First, they were classified as loss-of-function (LOF) or non-LOF mutations (7). The former group included nonsense and frameshift mutations that significantly disrupted p53 translation and caused LOF. The remaining mutations were classified in the non-LOF group. Secondly, mutations were divided into hot exon (exons 5–8) and non-hot exon (other exons) groups, according to whether or not the mutation was located on exons 5–8, which encode the DNA-binding domain and harbor most *TP53*-MUTs (8). The third system distinguished between disruptive and non-disruptive mutations. Disruptive mutations included terminating mutations and substitutions within the L2 or L3 binding domains with codons of amino acids of a different polarity or charge group (9). Disruptive mutations may lead to complete or almost complete p53 LOF, while non-destructive mutants can retain some functions. The final binary system classified patients into EAp53 high-risk (EAp53 score ≥75) and EAp53 low-risk groups (EAp53 score <75), in which EAp53 referred to the evolutionary

Table 1 Clinicopathological characteristics of patients with NSCLC

Characteristics	Number (%)
Subtype	
LUAD	566 (53.8)
LUSC	487 (46.2)
Gender	
Female	402 (38.2)
Male	597 (56.7)
NA	54 (5.1)
TNM stage	
I	514 (48.8)
II	282 (26.8)
III	166 (15.8)
IV	34 (3.2)
NA	57 (5.4)
Received neoadjuvant therapy	
No	991 (94.1)
Yes	8 (0.6)
NA	54 (5.1)
Received radiation therapy	
No	776 (73.7)
Yes	113 (10.7)
NA	164 (15.6)
Tumor diagnosis	
Recrudescence	547 (52.0)
New diagnosis	292 (27.7)
NA	214 (20.3)
Race	
American Indian or Alaska Native	1 (0.1)
Asian	17 (1.6)
Black or African American	81 (7.7)
White	725 (68.9)
NA	229 (21.8)
Survival	
No	396 (37.6)
Yes	605 (57.5)
NA	52 (4.9)

NSCLC, non-small cell lung cancer; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma.

action score of the *TP53* missense mutations (10). Higher scores indicated more harmful mutations (10). As EAp53 annotations could only be automated for approximately 50% of the *TP53*-MUTs in the dataset, the remaining mutations were annotated manually. In these cases, terminating, and frameshift mutations were defined as high-risk, and splice region mutations as low-risk.

Statistical analysis

Unpaired *t*-tests were used to compare continuous variables between the different binary groups. A Chi-squared test was used to compare the proportions of categorical variables between groups. Survival was illustrated using Kaplan-Meier curves, with P values determined by log-rank tests, and the hazard ratio (HR) and 95% confidence interval (CI) were determined by Cox regression models. All statistical tests were 2-tailed and were conducted in R (version 3.4.2, The R Foundation, https://www.r-project.org/). A 2-tailed P value of <0.05 was considered statistically significant.

Results

Clinical samples and histopathologic data

The baseline clinicopathological characteristics of the study cohort are shown in *Tables 1*,*2*. Of the 1,053 patients with NSCLC, 566 had LUAD and 487 had LUSC. Among them, 597 were male and 402 were female. Most patients did not receive neoadjuvant therapy (94.1%) or radiotherapy (73.7%). A cohort of patients with stage I–III NSCLC who underwent surgical treatment (n=931) was used to analyze survival time. This cohort consisted of 470 patients with LUAD and 461 with LUSC. Like the 1,053-patient cohort, most of these patients did not receive neoadjuvant therapy (99.1%) or radiotherapy (80.0%).

Rate and distribution of different classes of TP53-MUT

Of the patients with NSCLC, 63.2% (665 of 1,053) carried a *TP53*-MUT. The *TP53*-MUT rate was significantly lower in patients with LUAD (46.6%, 264 of 566) than in those with LUSC (82.3%, 401 of 487). No significant difference was observed in the distribution of *TP53*-MUTs between patients with LUAD and LUSC (*Figure 1*). In the four different binary systems, the LOF group was identified in 37.0% of patients with LUAD and 33.5% of those with LUSC (P=0.35); the hot exon group was identified in 72.5% of patients with LUAD and 76.1% with LUSC (P=0.30);

Table 2 Clinicopathological characteristics of patients with stage I–III NSCLC used for survival analysis

Characteristics	LUAD (%)	LUSC (%)	Overall
Total	470 (50.5)	461 (49.5)	931
Gender			
Female	257 (67.3)	125 (32.7)	382
Male	213 (38.8)	336 (61.2)	549
TNM stage			
I	271 (54.1)	230 (45.9)	501
II	119 (44.2)	150 (55.8)	269
III	80 (49.7)	81 (50.3)	161
T stage			
T1	159 (60.5)	104 (39.5)	263
T2	255 (48.7)	269 (51.3)	524
T3	43 (39.1)	67 (60.9)	110
T4	13 (38.2)	21 (61.8)	34
N stage			
N0	310 (51.4)	293 (48.6)	603
N1	87 (42.2)	119 (57.8)	206
N2	65 (62.5)	39 (37.5)	104
N3	2 (28.6)	5 (71.4)	7
NX	6 (54.5)	5 (45.5)	11
Neoadjuvant therapy			
No	467 (50.6)	456 (49.4)	923
Yes	3 (37.5)	5 (62.5)	8
Radiation therapy			
No	377 (51.9)	349 (48.1)	726
Yes	52 (50.5)	51 (49.5)	103
NA	41 (40.2)	61 (59.8)	102

LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma.

the disruptive group was identified in 50.7% of patients with LUAD and 48.8% with LUSC (P=0.65); and the EAp53 high-risk group was identified in 74.8% of patients with LUAD and 75.6% with LUSC (P=0.86).

Co-mutations

Most classic LUAD genomic alterations occurred more frequently in patients carrying *TP53*-MUTs than in those carrying the *TP53*-wildtype (*TP53*-WT) (*Figure 2A*): *EGFR*, 16.1% *vs.* 7.3%, respectively (P=0.001); *ALK*, 8.6% *vs.* 3.6%, respectively (P=0.02); v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*), 10.4% *vs.* 5.0%, respectively (P=0.02); and rearranged during transfection (*RET*), 6.8% *vs.* 1.0%, respectively (P=0.001). On the other hand, in patients with LUAD, *KRAS* mutations were less frequent among patients carrying a *TP53*-MUT than in those carrying the *TP53*-WT (21.8% *vs.* 33.7%, respectively; P=0.002) (*Figure 2B*). Specifically, patients carrying a *TP53*-MUT were significantly less likely to carry *KRAS* G12X than those carrying the *TP53*-WT (17.9% *vs.* 31.4%, respectively; P<0.001) (*Figure 2C*). Within the 8 classic NSCLC-associated driver genes and the 14 most frequently altered genes in patients with LUAD, the mutation rates of most genes were not significantly different when stratified according to the 4 *TP53*-MUT classification systems (Figure S1). Only mucin 16 (*MUC16*) was significantly more frequently altered among patients in the EAp53 high-risk group than among those in the low-risk group (58.0% *vs.* 41.2%, respectively; P=0.022) (Figure S1).

In patients with LUSC, the top 5 most frequently co-mutated genes were titin (*TTN*), CUB and Sushi multiple domains 3 (*CSMD3*), the type 2 ryanodine receptor (*RYR2*), low-density lipoprotein receptor-related protein 1B (*LRP1B*) and usher syndrome type IIA (*USH2A*). Their mutated rates were significantly higher in patients carrying a *TP53*-MUT than in those carrying the *TP53*-WT: *TTN* (78.7% *vs.* 44.6%; P<0.01), *CSMD3* (48.4% *vs.* 21.7%; P<0.01), *RYR2* (42.6% *vs.* 26.5%; P=0.009), *LRPB1* (38.8% *vs.* 18.1%; P<0.01), and *USH2A* (35.3% *vs.* 22.9%; P=0.038; *Figure 2D*). Subgroup analysis according to the *TP53*-MUT type showed that among the 25 most common genes in patients with LUSC, the mutation rates in patients carrying hot exon *TP53*-MUTs were significantly higher than in those with non-hot exon mutations for *LRPB1* (41.6% *vs.* 30.1%, respectively; P=0.049) and synaptic nuclear envelope protein 1 (*SYNE1*) (34.6% *vs.* 23.3%, respectively; P=0.044). In addition, *USH2A* was significantly more frequently altered in patients with non-disruptive *TP53*-MUTs than in those with disruptive *TP53*-MUTs (41.1% *vs.* 28.6%, respectively; P=0.009), and in patients in the EAp53 low-risk group compared to those in the EAp53 high-risk group (44.6% *vs.* 32.5%, respectively; P=0.036). The profiles of frequent alterations co-occurring with each type of *TP53*-MUT in patients with LUSC are presented in Figure S1.

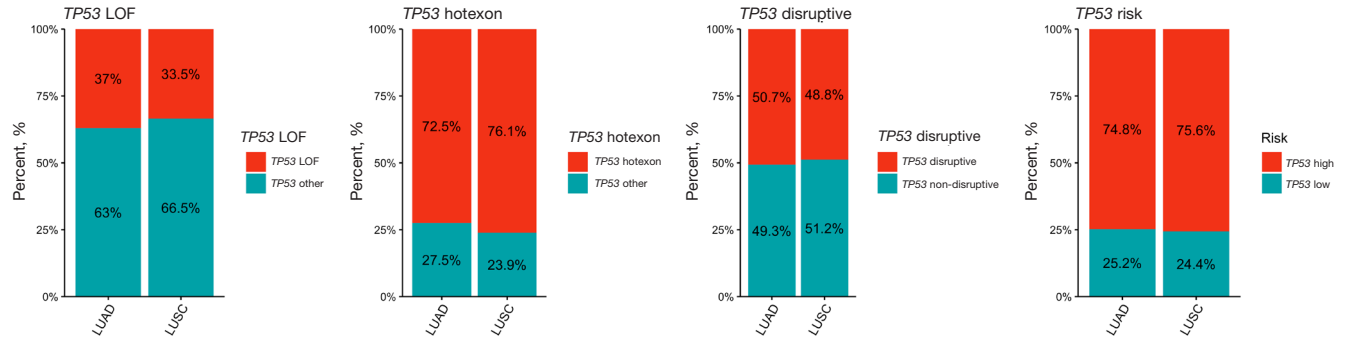

Figure 1 Percentages of patients with lung adenocarcinoma (LUAD) and squamous cell carcinoma (LUSC) carrying different classes of *TP53* mutations.

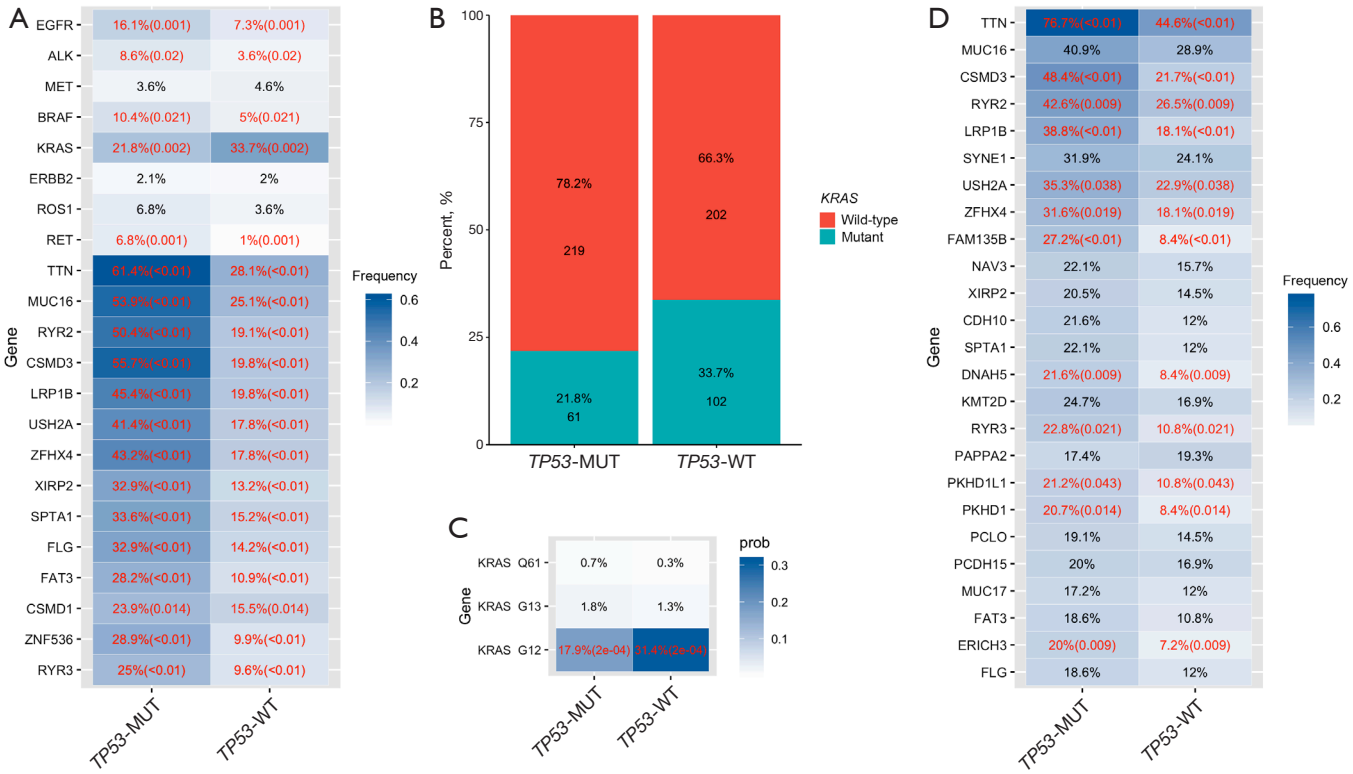

Figure 2 Differences of mutant genes between *TP53* mutant (*TP53*-MUTs) group and wild-type (*TP53*-WT) group in non-small cell lung cancer (NSCLC). (A) Mutation rates of 8 classic oncogenes in NSCLC and the 14 most frequently mutated genes in patients with lung adenocarcinoma (LUAD) carrying *TP53*-MUTs compared with *TP53*-WT. Significantly different rates (shown in red) are followed by the corresponding P values in parentheses; (B) mutation rates of Kirsten rat sarcoma viral oncogene (*KRAS*) in patients with LUAD carrying *TP53*-WT and *TP53*-MUTs; (C) mutation rates at the 3 most common *KRAS* hotspot codons in patients with LUAD; (D) mutation rates of the most frequently mutated genes in patients with lung squamous cell carcinoma (LUSC) carrying *TP53*-WT or a *TP53*-MUT.

Association between TP53-MUTs and the TMB

Overall, patients with NSCLC who carried a *TP53*-MUT showed a significantly higher TMB than those carrying the *TP53*-WT (6.0 *vs.* 2.6 mut/Mb, respectively; P<0.001) (*Figure 3A*). A similar distinction was observed in patients with LUAD, that patients carrying *TP53*-MUTs had a

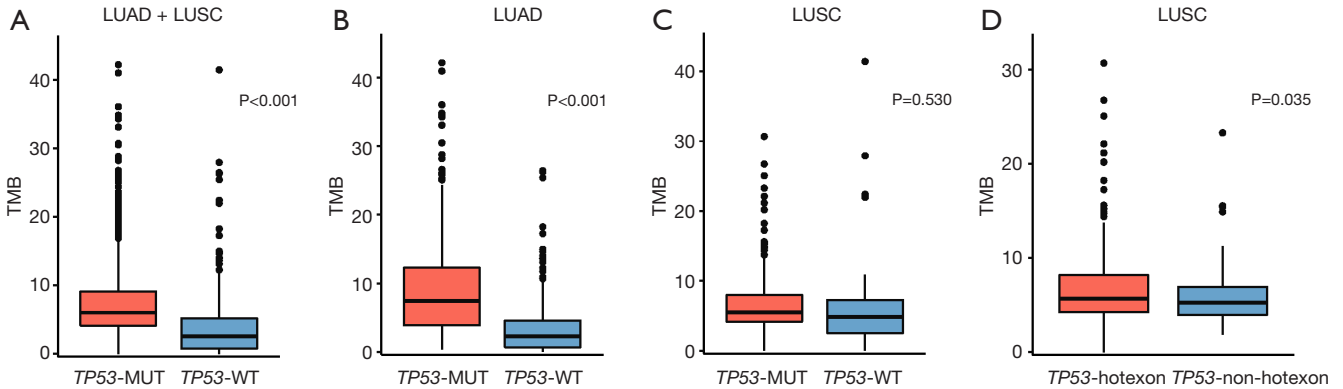

Figure 3 The tumor mutation burden (TMB) of patients carrying *TP53*-wild type (*TP53*-WT) and *TP53* mutations (*TP53*-MUTs) in (A) the entire cohort, (B) the lung adenocarcinoma (LUAD) subgroup, and (C) the lung squamous cell carcinoma (LUSC) subgroup. (D) TMB levels of patients with LUSC harboring *TP53* hot and non-hot exon mutations.

significantly higher TMB than those carrying the *TP53*-WT (7.4 *vs.* 2.3 mut/Mb, respectively; P<0.001) (*Figure 3B*), but the distinction was not observed in patients with LUSC (5.5 *vs.* 4.8 mut/Mb, respectively; P=0.53) (*Figure 3C*). In patients with LUSC carrying a *TP53*-MUT, subgroup analysis showed that the hot exon group had a significantly higher TMB than the non-hot exon group (5.7 *vs.* 5.2 mut/Mb, respectively; P=0.035) (*Figure 3D*). No significant difference was observed in pairwise comparisons of TMB levels in other *TP53*-MUT classifications for patients with either LUAD or LUSC (Figure S2).

Prognostic significance of different types of TP53-MUT in patients with stage I–III NSCLC who underwent surgery

Survival analysis of the 931 patients with stage I-III cancer who underwent surgery showed no significant difference in DFS between patients carrying the *TP53*-WT and those carrying a *TP53*-MUT, irrespective of the histologic subtype (Figures S3,S4). Subgroup analysis revealed no significant difference in DFS for patients with LUAD or LUSC who carried a *TP53*-MUT when stratified by any of the 4 *TP53*-MUT classification systems (Figures S3,S4).

In terms of OS, for patients with LUAD, no significant difference was found between patients carrying a *TP53*-MUT and those carrying the *TP53*-WT (49 *vs.* 54 months, respectively; P=0.13) (*Figure 4A*). In addition, we analyzed the prognostic relevance of the different types of *TP53*-MUTs. None of the 4 classes could significantly predict OS in patients with LUAD (*Figure 4B-4E*). However, in patients with LUSC, the OS was significantly longer for patients carrying a *TP53*-MUT than those carrying the *TP53*-WT (62 *vs.* 29 months, P=0.015; *Figure 5A*). Patients with LUSC carrying a non-LOF (P=0.014), hot exon (P=0.017), disruptive (P=0.0098), or EAp53 high-risk (P=0.0057) type of *TP53*-MUT all had longer OS than those carrying the *TP53*-WT (*Figure 5B-5E*). But no survival difference was observed between the counterpart groups of the four type methods. Multivariate analysis showed that a *TP53*-MUT was not an independent prognostic factor for OS in patients with stage I–III LUAD (HR =0.8, 95% CI: 0.57–1.1, P=0.192) (Figure S5), but was a good independent prognostic factor for OS in patients with stage I-III LUSC (HR =0.65, 95% CI: 0.44–0.95, P=0.028; *Figure 6*).

Discussion

TP53 is the most frequently altered gene in NSCLC, occurring in 35–55% of cases. Aberrant *TP53* is more prevalent in LUSC (~81%) than in LUAD (~46%) (11-13). The prevalence rate of *TP53*-MUTs in this study was 63.2% in NSCLC, 82.3% in LUSC, and 46.6% in LUAD. However, *TP53*-MUT rates were comparable within each classification systems (LOF *vs.* non-LOF, hot exon *vs.* non-hot exon, disruptive *vs.* non-disruptive, and EAp53 high-risk *vs.* EAp53 low-risk). There was a significant difference in the mutational landscape of *TP53*-MUTs in patients with LUAD and LUSC. Patients with LUAD carrying a *TP53*-MUT were more likely to harbor aberrant classic oncogenes such as *EGFR*, *ALK*, *BRAF*, and *RET*, whereas patients with LUSC carrying a *TP53*-MUT were more likely to harbor concurrent *TTN*, *CSMD*, *RYR2*,

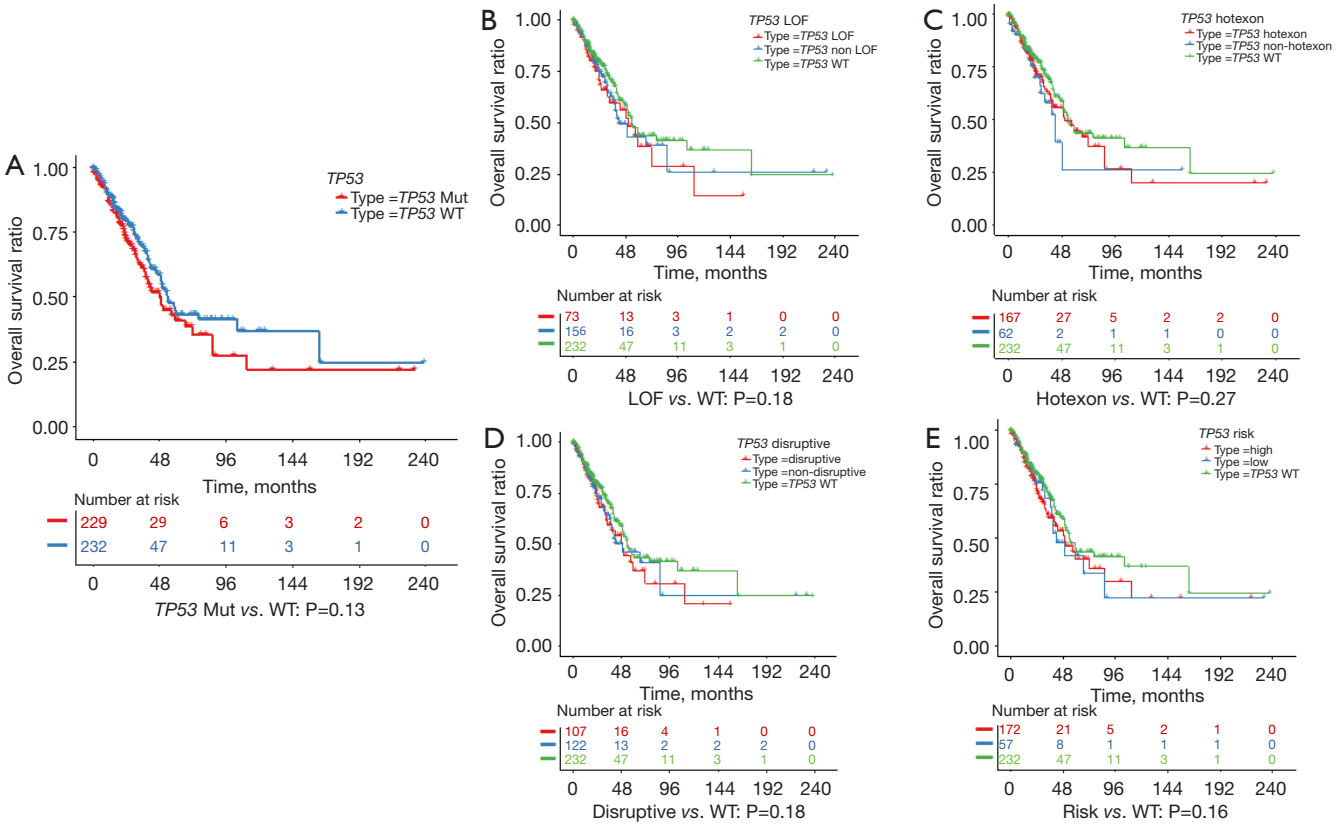

Figure 4 Kaplan-Meier survival plots showing the overall survival (OS) of patients with lung adenocarcinoma (LUAD), stratified by (A) *TP53* mutation (*TP53*-MUT) status or (B-E) different classes of *TP53*-MUTs.

LRP1B, and *DNAH5* mutations. Impacting carcinogenicity, co-mutations have become the core determinants in molecular and clinical heterogeneity of oncogene-driven NSCLC (14). *TP53*-MUT could be found in 30–72% of *EGFR*-mutated NSCLCs and 25–56% of *ALK*-positive NSCLCs (15). And *EGFR* mutation could be found in 10% of NSCLCs with *TP53*-MUT (16). No matter in patients with *EGFR* exon 19/21 or non-exon 19/21 mutation, *TP53*-MUT rate was higher than *EGFR* wild type patients (17). Co-mutated *EGFR* or *ALK* in patients carrying a *TP53*-MUT has been associated with a reduced response to tyrosine kinase inhibitors (TKIs), most likely because of increased genomic instability due to the aberrant *TP53* (15-18). On the other hand, *TP53*-MUT appeared to be mutually exclusive with mutations in certain genes, such as *KRAS*, and in particular with the hotspot mutation G12X. There is evidence associating *KRAS* and *TP53* co-mutation with poor clinical outcomes in patients with NSCLC, however, these patients may derive greater benefits from anti-PD-1/PD-L1 immunotherapy than patients who do not harbor *TP53* or *KRAS* mutation (19,20). *TP53*-MUTs can increase the expression of immune checkpoint proteins and activate the T-effector and interferon-γ signature. When both *TP53* and *KRAS* are altered, the expression of PD-L1 and the TMB increases significantly (19).

Several clinical studies have suggested a positive correlation between the survival of immunotherapy and the TMB of tumor (21-24). We found a significantly higher TMB in patients with LUAD carrying a *TP53*-MUT than in their *TP53*-WT-carrying counterparts. Some researchers have consistently found an increased proportion of *TP53*-MUTs in high TMB groups compared to low-to-medium TMB groups (25), as well as an increased TMB in patients carrying *TP53*-MUTs compared to those carrying *TP53*-WT (26,27). The stronger correlation between the TMB and *TP53*-MUTs in larger tumors, implicating the TMB and *TP53* in promoting tumor growth (27). Since the TMB is considered a powerful potential biomarker for immune checkpoint inhibitors, *TP53*-MUTs could contribute to predicting the benefits of immune checkpoint blockades.

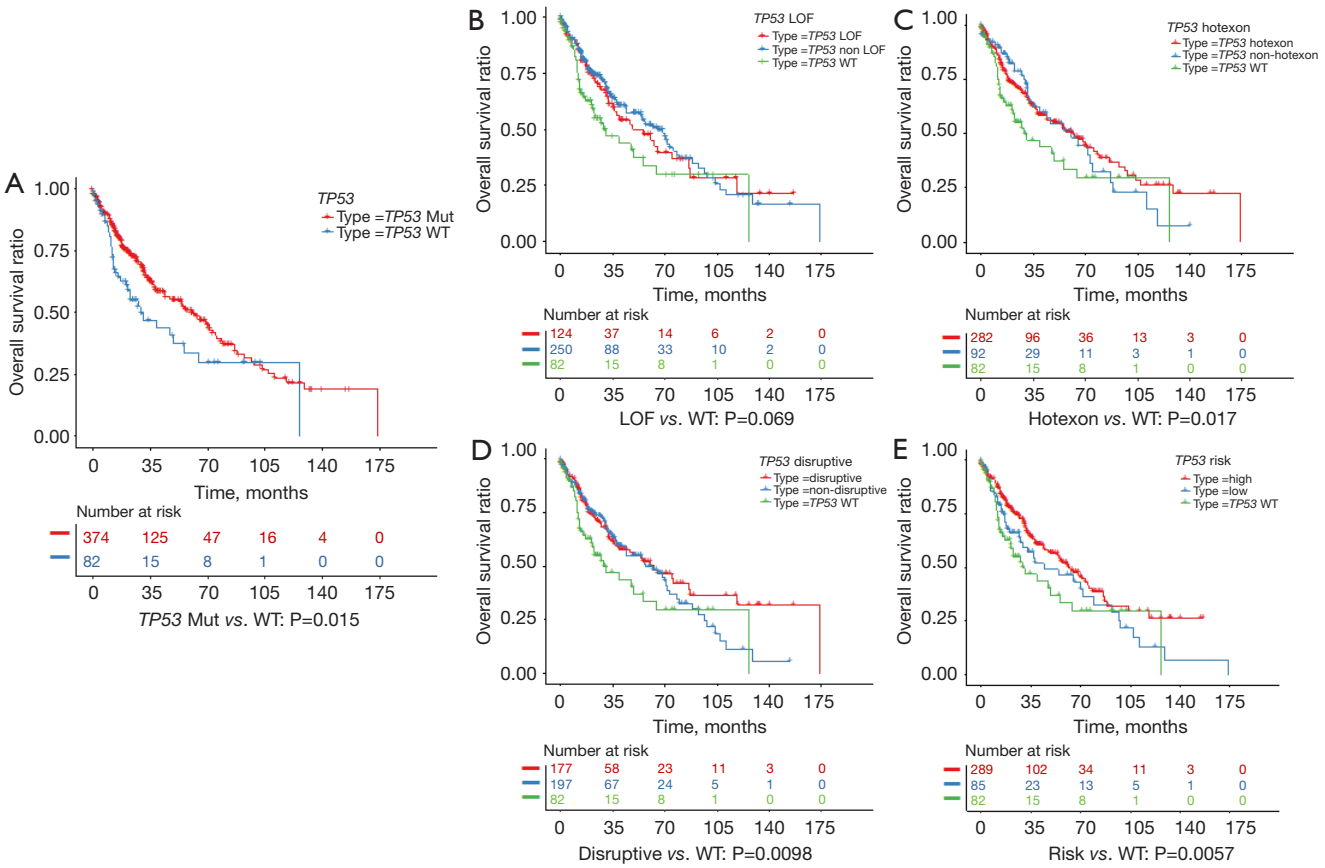

Figure 5 Kaplan-Meier survival plots showing the overall survival (OS) of patients with lung squamous cell carcinoma (LUSC), stratified by (A) *TP53* mutation (*TP53*-MUT) status or (B-E) different classes of *TP53*-MUTs.

In line with this association, evidence suggests that *TP53*-MUTs predict better OS benefited from immunotherapy in advanced NSCLC (28,29). More specifically, our analysis suggested that *TP53*-MUTs were significantly associated with the TMB in patients with LUAD but not in those with LUSC, which had not been previously reported. However, when comparing the different classes of *TP53*-MUTs, the TMB was significantly higher in the hot exon group than in the non-hot exon group for patients with LUSC. This correlation between *TP53*-MUTs and the TMB in patients with LUSC may have prognostic or therapeutic relevance. NSCLC patients carrying *TP53*-MUT have longer PFS for the immunotherapy than those carrying *TP53*-WT (30). The different expressed genes between LUSC with *TP53*-MUT and those with *TP53*-WT are closely related to immune functions indicating that genes related with *TP53*-MUT may interfere immunotherapy (31). Hot exon type of *TP53*-MUT may be helpful to find out patients with LUSC who can benefit from immunotherapy, and further clinical validation is warranted.

Many researches have shown that patients with NSCLC or LUAD carrying *TP53*-MUT have shorter OS than those carrying *TP53*-WT (11,26,32-34). However, whether *TP53*-MUTs shorten the survival of patients with LUSC is still lack of attention. Despite the similar DFS rates, patients in this study with stage I–III LUAD carrying a *TP53*-MUT had worse OS than those carrying the *TP53*-WT, although this difference did not reach statistical significance. In contrast, a *TP53*-MUT was a good independent prognostic factor for OS in patients with LUSC. Previous research into the prognostic impact of a *TP53*-MUT has focused mainly on patients with LUAD or NSCLC and seldom on those with LUSC (32-34). To the best of our knowledge, the present study is the first to show a significant association between favorable OS and *TP53*-MUTs in a large cohort of patients with LUSC. The opposing prognostic effects of *TP53*-MUTs for LUAD and LUSC suggested the p53 had different roles in the underlying biology of the 2 histologies,

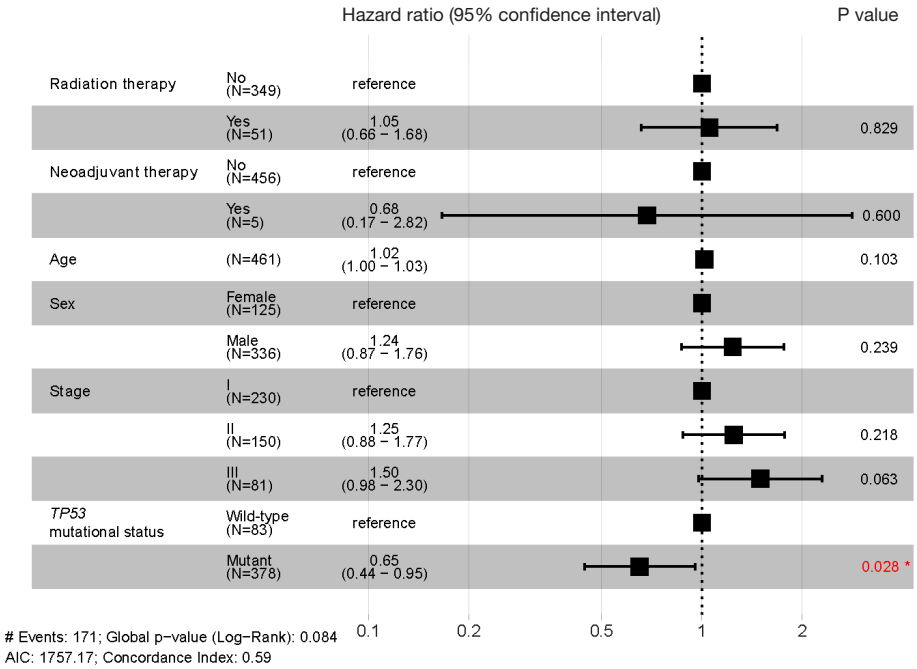

Figure 6 Multivariate analysis of prognostic factors for overall survival (OS) in patients with resectable stage I–III lung squamous cell carcinoma (LUSC) (n=461). *, P<0.05.

which should be considered in the decision-making process for NSCLC treatment.

We used 4 *TP53*-MUT classification methods to interrogate whether *TP53*-MUT types could lead to further stratification among patients carrying a *TP53*-MUT. For patients with LUAD, none of the subgroups showed different OS compared to patients carrying the *TP53*-WT, whereas for patients with LUSC, carriers of non-LOF, hot exon, disruptive, or EAp53 high-risk *TP53*-MUTs all manifested a lower risk of death compared with patients carrying the *TP53*-WT. Also, the EAp53 high-risk group showed a trend toward prolonged OS compared with the EAp53 low-risk group. Although little has been reported on the comparisons between the *TP53*-MUT subtypes, a few studies have examined the prognostic value of different *TP53*-MUT types by comparing their carriers to patients carrying the *TP53*-WT. For instance, in patients with stage I–III NSCLC receiving platinum-containing adjuvant chemotherapy, those carrying the hot exon *TP53*-MUTs showed a poorer prognosis than those with *TP53*-WT (35). The same was observed in patients with advanced *ALK*-rearranged NSCLC receiving crizotinib, an *ALK* TKI (36). In head and neck squamous cell carcinoma, patients in EAp53 high-risk groups have manifested poorer survival than those with *TP53*-WT (10). Another small-cohort study showed an association between EAp53 high-risk mutations and shorter recurrence-free survival (RFS) and OS, and an increased TMB compared with patients carrying EAp53 low-risk mutations or the *TP53*-WT (37). On the other hand, patients with NSCLC carrying the EAp53 low-risk *TP53*-MUT were also shown to have a significantly better OS rate than those carrying the EAp53 high-risk *TP53*-MUT or the *TP53*-WT (20). The median OS rate after initial diagnosis of metastasis was an impressive 64.5 months for the EAp53 low-risk *TP53*-MUT (20). Furthermore, the risk of death in patients carrying the EAp53 low-risk mutation was reduced by 70% and 48% when compared to those carrying the EAp53 high-risk mutation and the *TP53*-WT, respectively (20). Interestingly, when *KRAS* mutations coexistence, the survival advantage was absent in patients carrying EAp53 low-risk mutation, which illustrated the importance of the mutational landscape in prognostication (20). In this study, we observed the consistent prognostic effects of the EAp53 scoring system and, for the first time, applied this system to the survival analysis for NSCLC subtypes. EAp53 scores may currently be the most powerful prognostication tool for stratifying

patients carrying *TP53*-MUTs.

There were several limitations to our study. In this database-driven clinical investigation, we did not provide clear explanations for the underlying biological mechanisms for our findings. Also, these findings await future studies for further validation.

Conclusions

In summary, we characterized the distribution of mutation rates for various types of *TP53*-MUTs in patients with NSCLC, identified concurrent and mutually exclusive genomic alterations and revealed histology-specific differences in the OS of patients carrying a *TP53*-MUT. *TP53*-MUTs serve as a poor prognosis factor for patients with LUAD and a good prognosis factor for those with LUSC, raising the question of whether LUSC in patients carrying a *TP53*-MUT has a distinct etiology and should be considered as an atypical LUSC subtype. Findings from this study reinforce the relevance of *TP53*-MUTs in NSCLC prognostication and may aid the development of *TP53*-targeted therapy and the management of operable NSCLC.

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Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-412/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-412/coif). QZ was a student of Hebei medical university and studied in the Forth Hospital of Hebei medical university during the conduct of this study. XZ, YC and YS were employees of Burning Rock Biotech during the conduct of this study. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study does not involve ethical and moral constraints, and the data in this article are derived from public databases. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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