Original Article

Clinical features and prognostic biomarkers in patients with *SMARCA4*-mutated non-small cell lung cancer

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Background: Patients with non-small cell lung cancer (NSCLC) carrying *SMARCA4* mutations (*SMARCA4*-Mut) tend to have more advanced disease and a poor prognosis. However, due to the rarity of this mutation and the lack of related studies, the characteristics of *SMARCA4*-Mut NSCLC patients remains poorly determined. To clarify the clinical characteristics and prognostic factors of *SMARCA4*-Mut NSCLC, we initiated the present study to provide a clinical reference.

Methods: We used data from two cohorts of NSCLC-*SMARCA4*-mutated samples: The Cancer Genome Atlas (TCGA) database and our center's clinical data. The TCGA database was used to obtain 481 NSCLC-*SMARCA4*-Mut samples for clinical characterization. The center collected data on 224 consecutive NSCLC patients treated between December 2020 to July 2022. Among them, 26 harbored *SMARCA4* mutations, and 20 were eligible for inclusion in the study. Clinical, pathological, and molecular features, as well as prognostic role of *SMARCA4* mutations were analyzed. Additionally, we analyzed the prognostic impact of Napsin A expression in *SMARCA4*-Mut patients.

Results: The TCGA database included 480 patients with *SMARCA4*-Mut NSCLC, 311 males (64.8%) and 169 females (35.2%), with a median age of 67 years. Among the 20 *SMARCA4*-Mut patients in our center series, 12 (60%) were males and 8 (40%) females, with a median age of 63. The intergroup prognostic correlation analysis showed that *SMARCA4*-Mut patients had significantly worse prognosis than those the

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wild-type *SMARCA4* (*SMARCA4*-WT) (P=0.04). Within the *SMARCA4*-Mut group, patients with Napsin A expression had longer overall survival (OS) (P=0.03) than those without expression. Median survival in the Napsin A-positive and negative groups was 32 and 15 months, respectively. According to time-dependent receiver operating curve analysis, patients with Napsin A expression had significantly longer first-line treatment progression-free survival (PFS1) [area under the curve (AUC) =0.748] and OS (AUC =0.586). No prognostic value of Napsin A was found in patients *SMARCA4*-WT patients.

Conclusions: *SMARCA4*-Mut is an adverse prognostic feature in NSCLC patients. Napsin A expression in *SMARCA4*-Mut patients is associated with prolonged OS.

Keywords: Non-small cell lung cancer (NSCLC); *SMARCA4*; clinical features; Napsin A; prognosis

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Introduction

According to the 2022 estimates of the Global Cancer Observatory (GLOBOCAN), there were approximately 20 million new cases and 9.7 million cancer deaths worldwide, with lung cancer being the first most common cancer and the leading cause of cancer death (1). Non-small cell lung cancer (NSCLC), which accounts for 85% of lung cancer cases, is associated with low overall survival (OS) and high mortality (2). However, the prognosis of lung cancer varies according to the pathological type and molecular features (3,4).

SMARCA4 gene deletion is a special type of mutation typical for undifferentiated or poorly differentiated NSCLC and is associated with a high grade of malignancy (5). The *SMARCA4* gene, located in 19p13.2, encodes the protein BRG1, possesses ATPase activity, and is an important member of the BRG-/BRM-associated factor (BAF) chromosome regulatory complex regulating essential cell biological functions, such as DNA replication and repair, cell division, and differentiation (6). *SMARCA4*-mutated (*SMARCA4*-Mut) NSCLC was defined as a new pathological type of NSCLC in the 2021 edition of The WHO Classification of Thoracic Tumors.

SMARCA4 mutations (*SMARCA4*-Mut) have been reported to occur in about 10% of NSCLC cases, often in conjunction with other well-known lung cancer mutations such as those of *KRAS* and *TP53* (7,8). A study has shown that the median survival time of both *SMARCA4*-deficient undifferentiated tumors and *SMARCA4*-Mut non-small cell lung cancer (NSCLC-*SMARCA4*-Mut) is not ideal, with the former being only 5–7 months (9).

The clinical characteristics of *SMARCA4*-Mut NSCLC still need to be clarified due to the rarity of this population. We thus aimed to analyze the clinical characteristics and prognosis of patients with *SMARCA4*-Mut NSCLC by examining cases from The Cancer Genome Atlas (TCGA) database and clinical cases from the 900th Hospital of the Joint Logistic Support Force, People's Liberation Army of China. Additionally, in the latter group, we investigated the prognostic impact of aspartic peptidase (Napsin A), a crucial biomarker for classifying advanced NSCLC. At present there is no conclusive evidence about the association between *SMARCA4* and Napsin A. We combined the latest research reports and the content of this study to try to find new evidence of association between the two. We present this article in accordance with the REMARK reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-381/rc).

Highlight box

Key findings

- Patients with non-small cell lung cancer (NSCLC) with the *SMARCA4* mutation (*SMARCA4*-Mut) had a worse clinical prognosis than those with wild-type *SMARCA4*. Napsin A-positive expression in *SMARCA4*-Mut NSCLC was significantly associated with longer overall survival (OS).

What is known and what is new?

- Patients with NSCLC and *SMARCA4*-Mut are known to have a worse prognosis than those with the wild-type gene.
- Napsin A expression in *SMARCA4*-Mut patients is a favorable prognostic factor.

What is the implication, and what should change now?

- NSCLC patients with *SMARCA4*-Mut should be considered as a distinct entity.

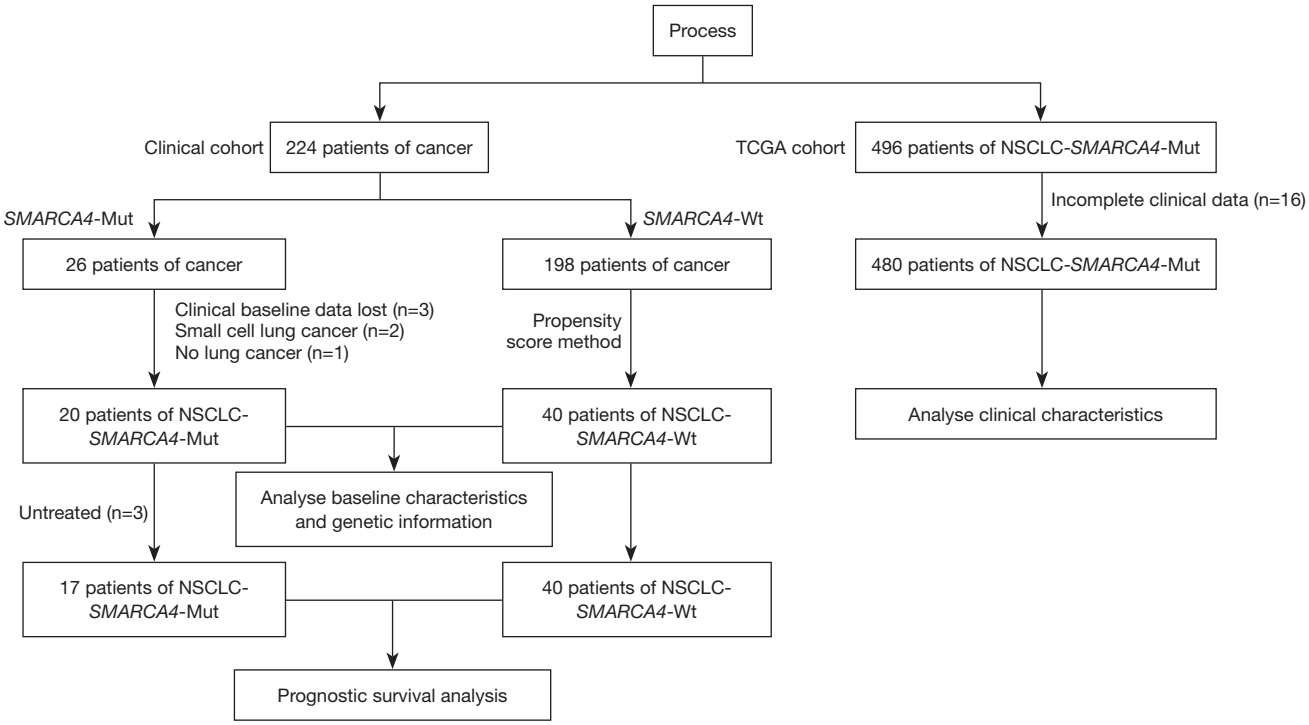

Figure 1 Consort diagram of study design and patient enrollment. TCGA, The Cancer Genome Atlas; NSCLC, non-small cell lung cancer; *SMARCA4*-Mut, *SMARCA4* mutation; *SMARCA4*-WT, *SMARCA4* wild type.

Methods

Patients

Between December 2020 and July 2022, we collected transcriptome and clinical data on NSCLC cancer cases with *SMARCA4*-Mut from the TCGA database (https://portal.gdc.cancer.gov/) to evaluate the clinical characteristics of *SMARCA4*-Mut NSCLC patients. The clinical baseline characteristics in this cohort included age, sex, smoking status, pathology, stage, tumor location, previous malignancy history, and treatment. Additionally, we retrospectively identified in the 900th Hospital of the Joint Logistic Support Force, People's Liberation Army of China database *SMARCA4*-Mut NSCLC cases to evaluate their clinical, pathological, and molecular features and to assess the prognostic value of *SMARCA4*-Mut (*Figure 1*). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Ethics Committee of the 900th Hospital of the Joint Logistic Support Force, People's Liberation Army of China (approval No. 2021-026). Informed consent was obtained from all individual participants included in the study. The inclusion criteria were as follows: (I) patients aged ≥18 years with histologically proven NSCLC; (II) patients subjected to next-generation sequencing (NGS) to detect 448 genes or 116 genes, encompassing tissue, blood, and pleural effusion; (III) treated according to the National Comprehensive Cancer Network (NCCN) guidelines.

The collected data included age, sex, smoking history, gene mutations, tissue type, imaging data [primarily computed tomography (CT) and magnetic resonance imaging (MRI) scans], immunohistochemistry (tissue specimen), tumor stage (based on the 8th TNM edition for lung cancer), and treatment. The primary treatment outcomes were OS and first-line treatment progression-free survival (PFS1). OS was defined as the time from the date of diagnosis to the last follow-up and/or death from any causes, while PFS1 was defined as the time from the administration of first-line drug therapy to the date when the first progressive disease (PD) was confirmed. The data cut-off date was on April 30, 2023.

Biopsy tissue specimens were fixed, embedded, sectioned, antigenically repaired, closed, incubated, enzyme-substrate chromogenic or fluorescence detected, and sealed. Additionally, we determined the Napsin A expression using two categories: negative (Napsin A not detected) and

Table 1 Clinicopathological parameters of patients with the *SMARCA4* mutation (TCGA cohort)

Characteristics	*SMARCA4* mutation group (N=480)
Age (years)	
≥18–<60	112 (23.3)
≥60–<75	282 (58.8)
≥75–<85	81 (16.9)
≥85	5 (1.0)
Gender	
Male	311 (64.8)
Female	169 (35.2)
Smoking status	
Smoker	374 (77.9)
Never smoker	106 (22.1)
Histology	
Squamous cell carcinoma	230 (47.9)
Adenocarcinoma	248 (51.7)
Other[†]	2 (0.4)
Stages[‡]	
IA	104 (21.7)
IB	137 (28.5)
IIA	61 (12.7)
IIB	82 (17.1)
IIIA	63 (13.1)
IIIB	15 (3.1)
IV	18 (3.8)
Primary tumor site	
Upper lobe	277 (57.7)
Lower lobe	157 (32.7)
Lung, not specified	21 (4.4)
Middle lobe	14 (3.0)
Main bronchus	5 (1.0)
Overlapping lesion	5 (1.0)
Pleura	1 (0.2)
Prior malignancy	
Yes	82 (17.1)
No	398 (82.9)
Treatment type	
Pharmaceutical	256 (53.3)
Radiation	224 (46.7)

Data are presented as n (%). [†], small cell, signet ring cell carcinoma, not otherwise specified; [‡], TNM staging of lung cancer (8th edition). TCGA, The Cancer Genome Atlas.

positive (Napsin A detected). The study was retrospective and not blinded.

Bioinformatic analysis

Second-generation DNA sequencing was performed with a 448-gene panel and NextSeq 500 system (Illumina Inc., San Diego, CA, USA), which is primarily used for mutation diagnosis in lung and bowel cancers. Finally, bioinformatics and sequencing data were analyzed using the ADXLC10 module of the AmoyDx NGS data analysis system (Amoy Diagnostics Amoy Diagnostics Co., Ltd., Shanghai, China).

Statistical analysis

Statistical analysis was conducted using SPSS Statistics 26.0 software (IBM Corp.). Chi-squared tests or Fisher exact tests were employed to compare the categorical data between the groups. Survival estimates were calculated using the Kaplan-Meier method and compared using the log-rank test. Time-dependent receiver operating characteristic (ROC) curve analysis was used to evaluate the prognostic value of the indicators, and the Cox proportional hazard regression model was used to determine the prognostic factors for OS. All statistical tests were two-sided, and a P value <0.05 was considered statistically significant. GraphPad Prism 9.5.0 (GraphPad Software) was used to generate the survival curve and ROC curve.

Results

Clinicopathological characteristics of the TCGA cohort

A total of 496 cases of *SMARCA4*-Mut were initially selected from the TCGA database. Of these, 16 cases with incomplete clinical data were excluded, resulting in a final cohort of 480 cases.

The median age in the *SMARCA4*-Mut TCGA cohort was 67 years (*Table 1*). A total of 311 patients (64.8%) were males, and 374 (77.9%) were smokers. Among them, 248 (51.7%) were adenocarcinomas and 230 (47.9%) were squamous cell carcinomas. In 277 cases (57.7%) the primary tumor was located in the upper lobe, and in 157 (32.7%) in the lower lobe of the lung.

Clinicopathological characteristics of clinical cohort

In our retrospective clinical series, 26 of 224 patients had

Table 2 Patient characteristics (retrospective cohort)

Characteristics	*SMARCA4*-Mut group (N=20), n (%)	*SMARCA4*-WT group (N=40), n (%)	P value
Age (years)			0.46
<65	11 (55.0)	18 (45.0)	
≥65	9 (45.0)	22 (55.0)	
Average [range]	60.15 [34–76]	61.38 [30–85]	
Gender			0.71
Male	12 (60.0)	26 (65.0)	
Female	8 (40.0)	14 (35.0)	
Smoking status			0.55
Smoker	7 (35.0)	11 (27.5)	
Never	13 (65.0)	29 (72.5)	
Lymph node metastasis			>0.99
Yes	16 (80.0)	32 (80.0)	
No	4 (20.0)	8 (20.0)	
Histology			0.20
Adenocarcinoma	14 (70.0)	32 (80.0)	
Squamous cell carcinoma	2 (10.0)	6 (15.0)	
Other[†]	4 (20.0)	2 (5.0)	
Stage			0.21
I–III	3 (15.0)	12 (30.0)	
IV	17 (85.0)	28 (70.0)	
Pleural effusion			0.35
Yes	6 (30.0)	11 (27.5)	
No	14 (70.0)	29 (72.5)	
EGFR			0.85
Non-mutated	8 (40.0)	17 (42.5)	
Mutated	12 (60.0)	23 (57.5)	

[†], large cell lung carcinoma with neuroendocrine features, *SMARCA4* undifferentiated lung cancer, undifferentiated lung cancer, sarcomatoid lung carcinoma (one case each). *SMARCA4*-Mut, *SMARCA4* mutation; *SMARCA4*-WT, *SMARCA4* wild type; EGFR, epidermal growth factor receptor.

SMARCA4-Mut and 20 (12 males and 8 females) were eligible for this study, with a median age of 63 years. The control group included 40 NSCLC patients with wild-type *SMARCA4* (*SMARCA4*-WT) diagnosed and treated at our institution during the same period, matched using the propensity score method (1:2 ratio), matching variables including sex, age, smoking status, and pathology type, to ensure that the baseline data are consistent between the two groups.

Hence, a total of 60 patients were analyzed as the clinical cohort. There were no significant differences between both groups in terms of age, sex, smoking status, tumor stage, lymph node metastasis, Histology, or pleural effusion (*Table 2*).

The most common mutations in both groups were in *EGFR*, *TP53*, *AXIN2*, *SPTA1*, and *CDH1* genes. *SETBP1* and *SPEN* were more frequently mutated in the *SMARCA4*-

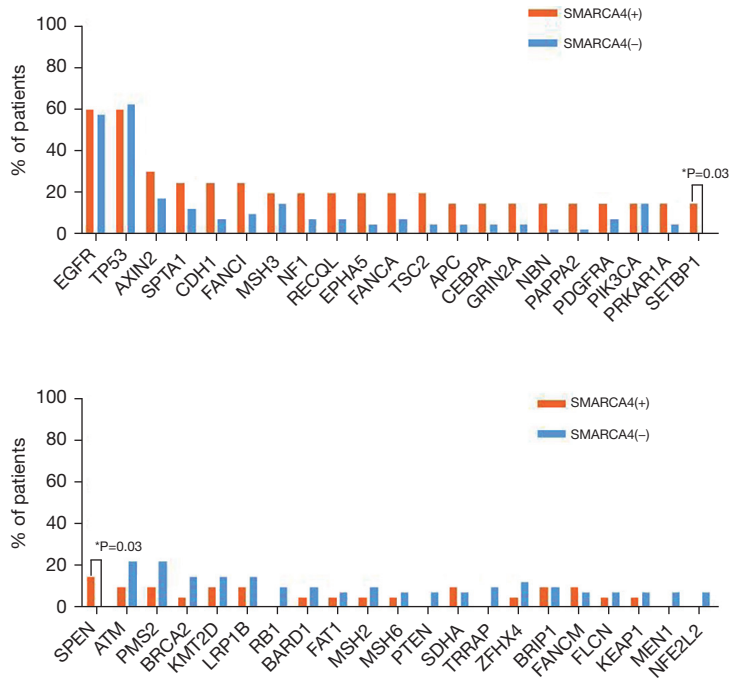

Figure 2 Gene mutations in the *SMARCA4*-Mut and *SMARCA4*-WT groups. Red represents mutant, and blue represents wild-type. The chi-squared test was used to compare the proportion of each group harboring the listed mutations. *, P<0.05, difference statistically significant. *SMARCA4*(+), *SMARCA4* mutation; *SMARCA4*(–), *SMARCA4* wild type; *SMARCA4*-Mut, *SMARCA4* mutation; *SMARCA4*-WT, *SMARCA4* wild type.

Mut than in the *SMARCA4*-WT group (P=0.03) (*Figure 2*). In the *SMARCA4*-Mut nonSynonymous_Substitution 7 cases, Synonymous_Substitution 5 cases, intronic 4 cases, Nonsense_Mutation 3 cases, Splicing 1 case. OncoGrid was used to illustrate the frequencies, including a composite of all alterations (5' untranslated region, frameshift mutation, intronic, non-frameshift mutation, nonsense mutation, splicing, and synonymous substitution) (*Figure 3*).

Prognostic value of SMARCA4-Mut

We excluded from the analysis three cases with no treatment and no survival data in the *SMARCA4*-Mut group. Thus, prognostic correlation analysis was performed in 17 cases with *SMARCA4*-Mut and 40 with *SMARCA4*-WT.

Kaplan-Meier curves were used to analyze whether there was a difference in prognosis between the *SMARCA4*-Mut and *SMARCA4*-WT groups. There was a significant difference between the groups in terms of OS (P=0.04) (*Figure 4*). Consequently, we analyzed the overall samples OS using the Cox proportional risk model. The risk of death in the univariate analysis was statistically higher in the *SMARCA4*-Mut group (P=0.046) and was in the multivariate analysis (P=0.03) (*Figure 5*). This suggests that *SMARCA4*-Mut increases patients' risk of death, significantly impacting their OS.

Prognostic value of Napsin A expression according to SMARCA4-Mut

In this series, Napsin A expression was less common in the *SMARCA4*-Mut compared to the *SMARCA4*-WT NSCLC group (58.8% *vs.* 65%, respectively), but the difference was insignificant *(Table 3)*.

In the entire group, Napsin A expression was not significantly associated with PFS1 (P=0.63) and OS (P=0.49) (*Figure 6*). Therefore, we conducted an analysis of the *SMARCA4*-Mut group and *SMARCA4*-WT group. There was a statistically significant in OS (P=0.03) between Napsin A-positive and negative patients in the *SMARCA4*-Mut group (*Figure* 7). We thus speculated that Napsin A might play a more critical role in the prognosis of *SMARCA4*-Mut NSCLC.

To further explore the prognostic value of Napsin A,

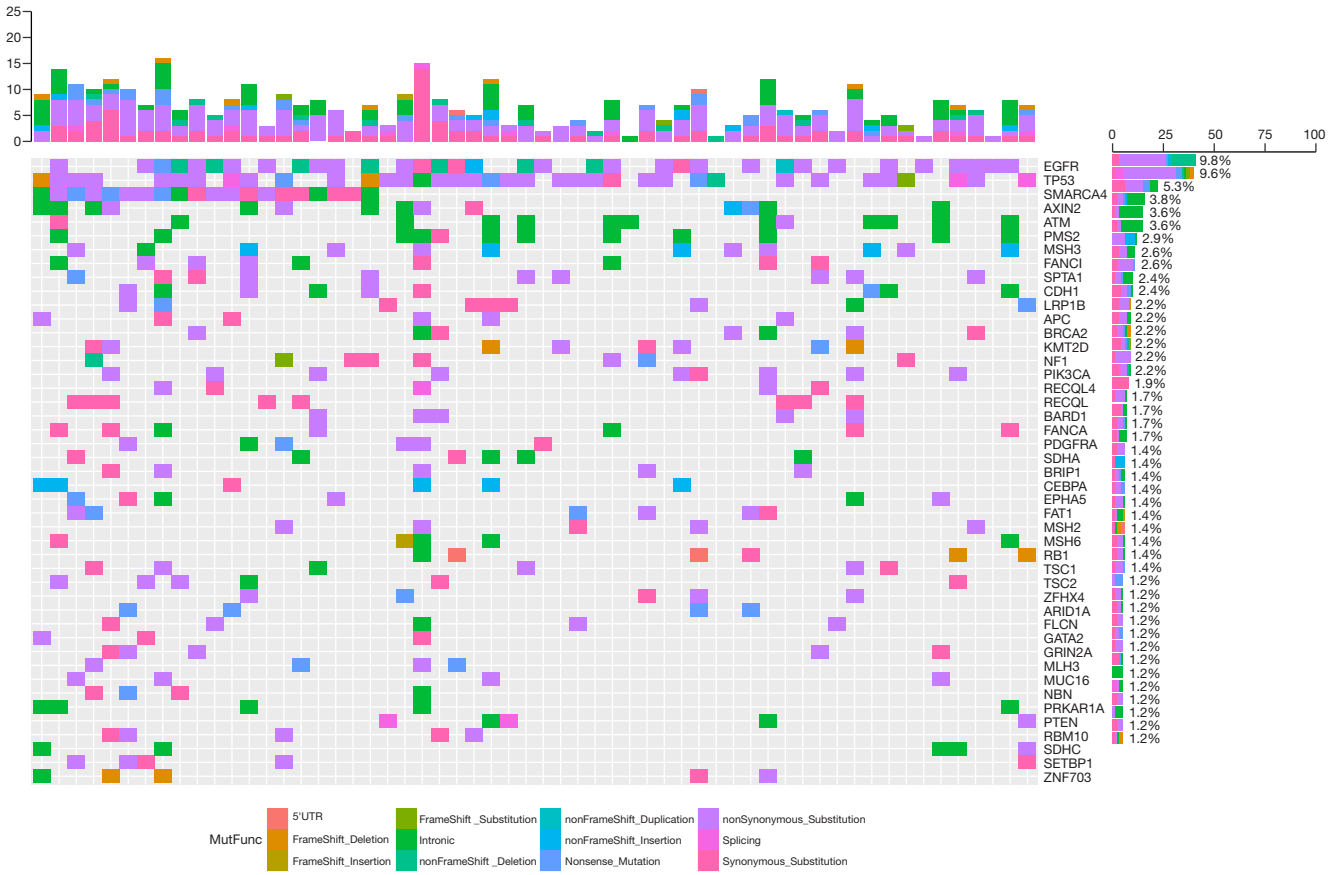

Figure 3 Mutations in the *SMARCA4*-Mut and *SMARCA4*-WT groups (60 samples), with the first 20 datasets representing the mutant group and the last 40 representing the wild-type group. The mutation frequency for each gene and each subtype is shown as a percentage of the total mutation type. Different colors represent various mutation types. X axe, frequency of mutations in 1 gene/frequency of mutations in all genes; Y axe, number of mutated genes (1 patient)/total number of mutated genes. *SMARCA4*-Mut, *SMARCA4* mutation; *SMARCA4*-WT, *SMARCA4* wild type.

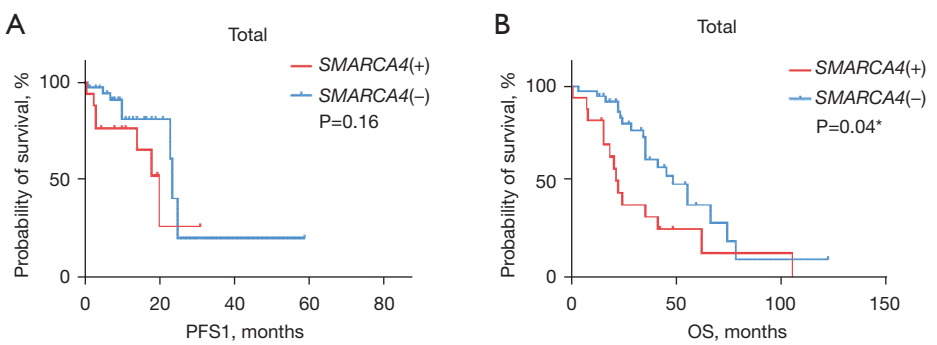

Figure 4 Kaplan-Meier curves for PFS1 and OS in the *SMARCA4*-Mut and *SMARCA4*-WT groups in the whole sample. (A) PFS1 data. (B) OS data. *, P<0.05, difference statistically significant. *SMARCA4*(+), *SMARCA4* mutation; *SMARCA4*(–), *SMARCA4* wild type; *SMARCA4*-Mut, *SMARCA4* mutation; *SMARCA4*-WT, *SMARCA4* wild type; PFS1, first-line treatment progression-free survival; OS, overall survival.

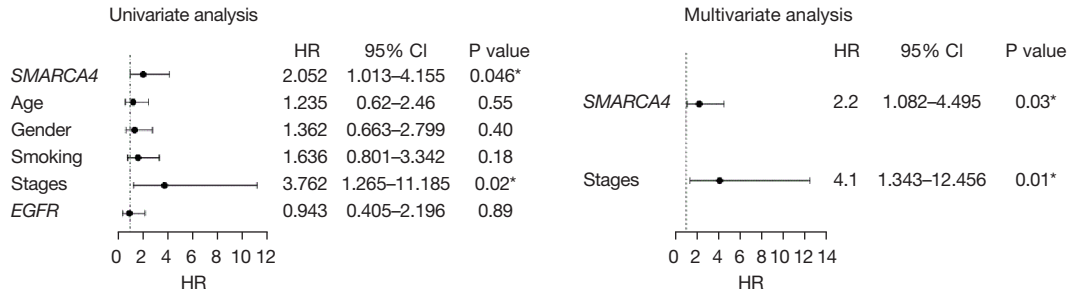

Figure 5 Prognostic factors (Cox proportional hazards model). *, P<0.05, difference statistically significant. *EGFR*, epidermal growth factor receptor; HR, hazard ratio; CI, confidence interval.

Table 3 Immunohistochemistry and treatment of patients

Characteristics	*SMARCA4*-Mut group (N=17), n (%)	*SMARCA4*-WT group (N=40), n (%)	P value
Napsin A			0.66
Negative	7 (41.2)	14 (35.0)	
Positive	10 (58.8)	26 (65.0)	
First-line treatment			0.95
Targeted therapy	9 (52.9)	23 (57.5)	
Chemotherapy + immunotherapy	6 (35.3)	13 (32.5)	
Nonpharmacological treatments	2 (11.8)	4 (10.0)	

SMARCA4-Mut, *SMARCA4* mutation; *SMARCA4*-WT, *SMARCA4* wild type.

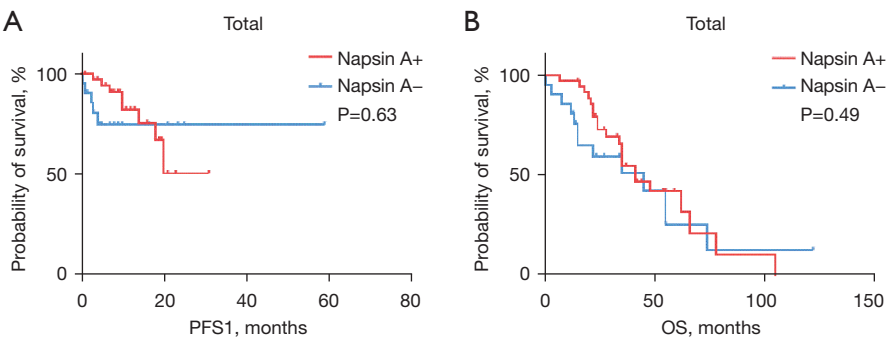

Figure 6 Kaplan-Meier curves for the PFS1 and OS in the Napsin A-positive and negative groups for the all patients. (A) PFS1 data. (B) OS data. Napsin A+, Napsin A-positive; Napsin A–, Napsin A-negative; PFS1, first-line treatment progression-free survival; OS, overall survival.

we used time-dependent receiver operating characteristic (time-dependent ROC) curves to predict the impact of Napsin A expression in the *SMARCA4*-Mut and the *SMARCA4*-WT groups. In the *SMARCA*4-Mut group, the area under the curve (AUC) value for PFS1 and OS were 0.748 and 0.586, respectively, and in the *SMARCA4*-WT group, 0.360 and 0.152, respectively, further supporting the hypothesis of favorable prognostic impact Napsin A expression in *SMARCA4*-Mut patients (*Figure 8*).

Discussion

The clinical features of *SMARCA4*-Mut patients in our clinical sample were similar to those in the TCGA cohort and previous series, considering age, sex, and smoking status. A previous study has indicated that thoracic

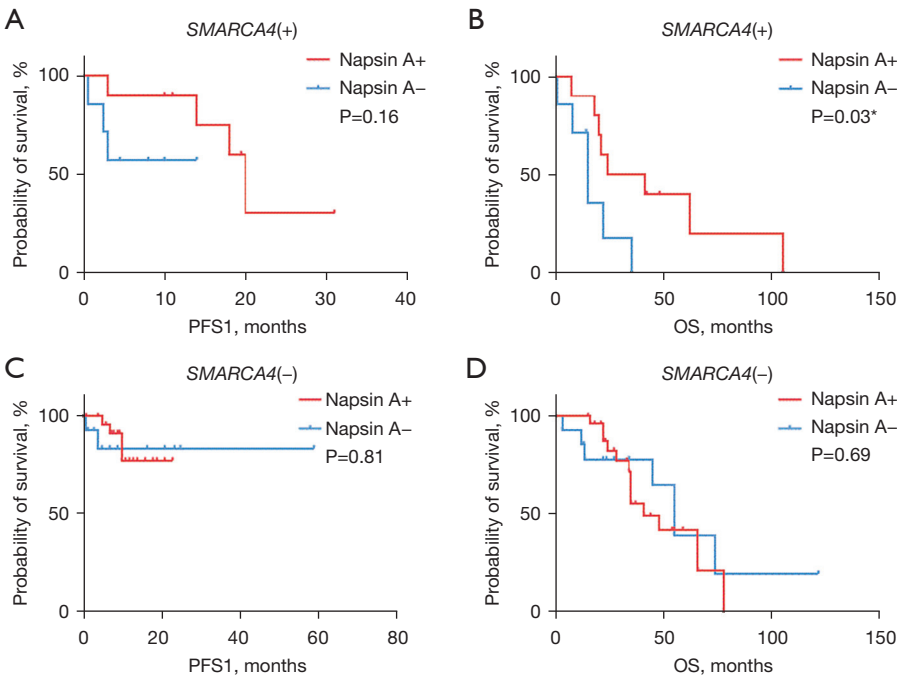

Figure 7 PFS1 and OS for Napsin A-positive and negative groups in the *SMARCA4*-mutant and the *SMARCA4*-WT group. (A) PFS1 for Napsin A-positive and negative groups in the *SMARCA4*-mutant group. (B) OS for Napsin A-positive and negative groups in the *SMARCA4*-mutant group. (C) PFS1 for Napsin A-positive and negative patients in the *SMARCA4*-WT group. (D) OS for Napsin A-positive and negative patients in the *SMARCA4*-WT group. *, P<0.05, difference statistically significant. PFS1, first-line treatment progression-free survival; OS, overall survival; *SMARCA4*(+), *SMARCA4* mutation; *SMARCA4*(–), *SMARCA4* wild type; Napsin A+, Napsin A-positive; Napsin A–, Napsin A-negative; *SMARCA4*-Mut, *SMARCA4* mutation; *SMARCA4*-WT, *SMARCA4* wild type.

SMARCA4-deficient undifferentiated tumors are most likely to occur in adults, with a median age of 48 years (ranging from 27 to 90 years), and are significantly more common in males, particularly heavy smokers (10). *SMARCA4*-deficient NSCLC, a smoking-related undifferentiated or differentiated invasive lung cancer, is predominantly observed in young men with a median age of 63 years and is associated with a high incidence of pleural and vascular infiltration (11).

SMARCA4-Mut NSCLC has been shown to have increased abundances of lymphocytes, macrophages, and multinucleated giant cells, corresponding to an increase in inflammatory cells in the surrounding tumor stroma. The Switch defective/sucrose non-fermentable (SWI/SNF) complex, to which *SMARCA4* belongs, has been identified as an immune system modulator. A study has demonstrated that *SMARCA4* is a core gene that critically contributes to tumorigenesis by regulating the tumor microenvironment (TME) through both cell autonomy and TME interactions (12). Patients with *SMARCA4*-Mut NSCLC have a poor prognosis, especially those with truncated, fusion, and homozygous deletion. In turn, *SMARCA4*-Mut NSCLC, particularly with the last mutation type, may be more sensitive to immune checkpoint inhibitors (ICIs) (7). Several cases of successful ICI treatment for advanced *SMARCA4*-deficient NSCLC and *SMARCA4*-deficient malignant rhabdomyoma-like tumors have been reported (8,13).

In our series, *SMARCA4*-Mut, compared with *SMARCA4*-WT tumors, more frequently carried mutations in two genes (*SETBP1*, *SPEN*), associated with sensitivity to ICI. The *SETBP1* gene, present in approximately 13% of patients with lung adenocarcinomas (LUAD), is one of the signatures LUAD mutations, alongside that of *KEAP1* and *STK11*, and carries an adverse prognosis. Low-level expression of SETBP1 induces epithelial-mesenchymal transition (EMT) through the ERK1/2 signaling pathway, promoting proliferation, migration, and invasion of NSCLC cells. SETBP1 expression is significantly correlated with the regulation of tumor-infiltrating immune cells, especially M1 macrophages (14). M1 macrophages are

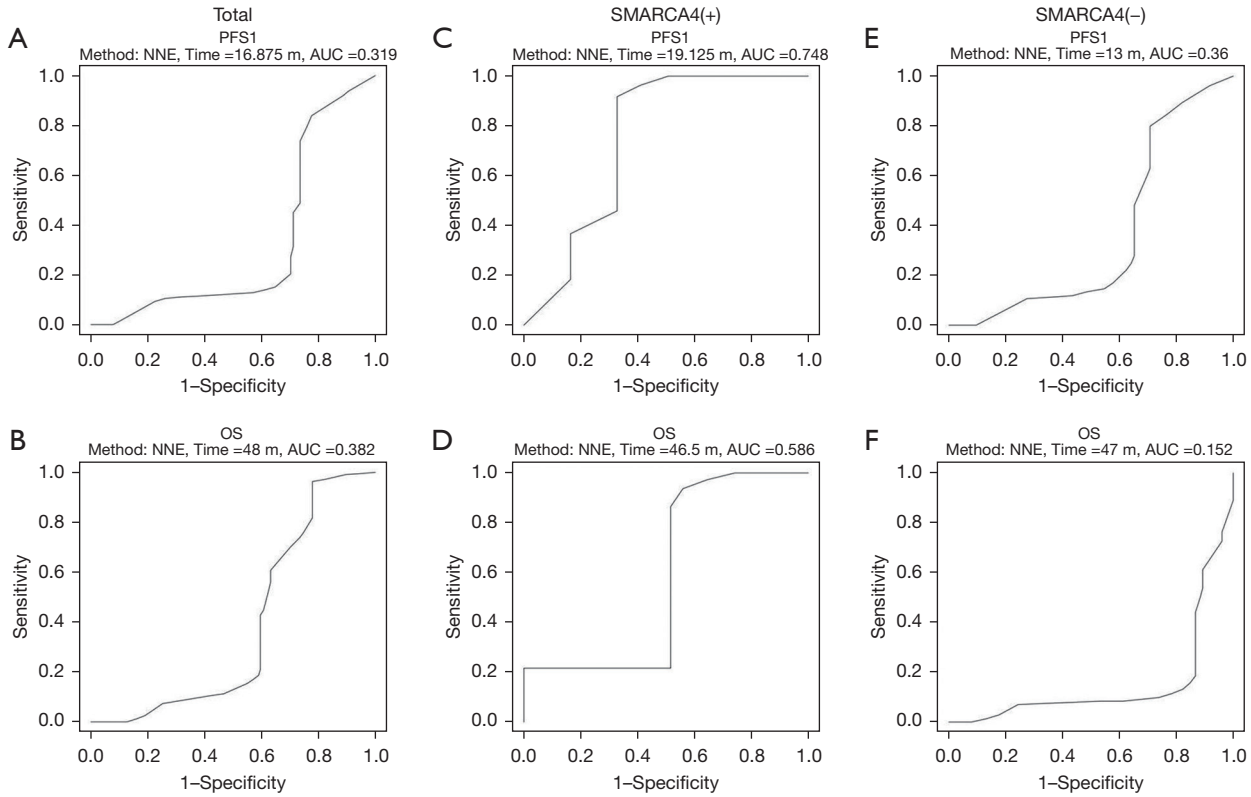

Figure 8 Area under the time-dependent ROC curve for the accuracy of predicting OS according to Napsin A expression. (A,B) All patients. (C,D) *SMARCA4*-Mut group. (E,F) *SMARCA4*-WT group. A, C, E represent PFS1, and B, D, F represent OS. NNE, Nearest Neighbor Estimation; m, months; AUC, area under the curve; PFS1, first-line treatment progression-free survival; OS, overall survival; *SMARCA4*(+), *SMARCA4* mutation; *SMARCA4*(–), *SMARCA4* wild type; *SMARCA4*-Mut, *SMARCA4* mutation; *SMARCA4*-WT, *SMARCA4* wild type; ROC, receiver operating characteristic.

associated with a poor prognosis for lung cancer (15). This study also found that CD1^{+}T cells, CD, and monocytes were negatively correlated with SETBP1 expression levels. *SPEN* is a tumor-suppressor gene, and its mutations are an adverse prognostic feature in small-cell lung cancer (16). However, *SPEN* mutation was associated with better OS in a pan-cancer cohort of patients administered ICI (17).

Another finding of our study is a favorable prognostic impact of Napsin A expression in *SMARCA4*-Mut patients. Napsin A, belonging to the peptidase A1 family, is a single-chain protein with a molecular weight of 45 kDa, composed of 420 amino acids encoded by the *NSPSA* gene on chromosomal body 19q13.3.45. In the lung, Napsin A is primarily expressed in alveolar type II epithelial cells and in alveolar macrophages. Napsin A is an important biological indicator in typing of advanced NSCLC and a more sensitive marker of LUAD. The loss of *SMARCA4* plays a paradoxical role in tumor development, inhabiting tumor progression in early tumors and accelerating at the highly advanced stages (18,19). The reason for this is that most transformed cells carrying *SMARCA4*-Mut are alveolar type II (ATII) cells, which gradually transform into club cells at the later stage of tumor development and are sensitive to malignant transformation and tumor progression in a cell type-dependent manner (20). We hypothesized that the effect of Napsin A may be related to the transformation of ATII cells in the cancer occurrence and development. High expression of Napsin A predicted a higher proportion of *SMARCA4*-Mut ATII cells, which in turn was associated with slower tumor progression, leading to prolonged survival.

For the first time, we analyzed the prognostic impact of Napsin A expression in relation to *SMARCA4*-Mut. Napsin A, belonging to the peptidase A1 family, is a single-chain protein with a molecular weight of 45 kDa, composed of 420 amino acids encoded by the *NSPSA* gene on chromosomal body 19q13.3.45. In the lung, Napsin

A is primarily expressed in alveolar type II epithelial cells and is also present in alveolar macrophages. Napsin A is an important biological indicator in the typing of advanced NSCLC. This protein is mainly expressed in LUAD, whereas *SMARCA4*-Mut occurs in all pathological types of NSCLC. Napsin A positive expression is associated with a lower grade of malignancy and slower tumor progression (21,22).

Our results indicate that the expression of Napsin A correlates with a better prognosis in patients with *SMARCA4*-Mut but not in those with *SMARCA4*-WT. This may also refer to the pathological type.

SMARCA4 deficiency leads to decreased expression of inositol 1,4,5-triphosphate receptor (IP3R3), resulting in impaired Ca^{2+} transfer from the endoplasmic reticulum to the mitochondria, required for apoptosis induction (23). In turn, SWI/SNF complexes regulate nutrient sensing and energy metabolism during normal development (24). The GLUT1/SLC38A2-mediated metabolic shift may be due to *SMARCA4/2* loss. GLUT1 deficiency induced by *SMARCA4/2* loss is a key contributor to the oxidative phosphorylation dependency in the *SMARCA4/2*-deficient cancer cells, and *SMARCA4/2*-deficient NSCLC cells express the lowest levels of GLUT1 (25). As discussed earlier, the ICI benefits associated with various mutations, and the expression of key cell groups and metabolic components in the TME also impact treatment outcomes. *SMARCA4*-Mut tumors are coregulated by multiple key factors, and Napsin A may affect only one.

Conclusions

SMARCA4-Mut is an adverse prognostic feature in NSCLC patients. Napsin A expression in *SMARCA4*-Mut patients is associated with prolonged OS. However, we are aware of several limitations of our study, the most important of which are its retrospective type, small patient sample, and treatment heterogeneity. Thus, the clinical relevance of *SMARCA4*-Mut in NSCLC warrants further investigation.

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Footnote

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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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved granted by the Institutional Ethics Committee of the 900th Hospital of the Joint Logistic Support Force, People's Liberation Army of China (No. 2021-026). Informed consent was obtained from all individual participants included in the study.

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