

Tumor-Associated Autoantibodies Anti-p53 is Associated with Poor Prognosis in Patients with Lung Adenocarcinoma

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Purpose: There is a known association between tumor-associated autoantibodies (TAABs) and lung cancer. TAABs are currently used in clinical settings for the early detection of lung cancer. However, the relationship between TAABs profiles and clinical outcomes in lung cancer patients remains incompletely understood. This study aims to investigate the association between TAABs and survival rates in individuals diagnosed with lung adenocarcinoma.

Patients and Methods: This study enrolled 161 patients diagnosed with lung adenocarcinoma at Henan Province People's Hospital between January 2020 and December 2022. Levels of TAABs were measured using a commercial enzyme-linked immunosorbent assay (ELISA) kit. Follow-up data were collected through December 2024. The association between TAABs levels and disease progression was evaluated using Kaplan–Meier survival analysis and Cox proportional hazards models.

Results: In the univariate analysis, the presence of p53 autoantibodies (anti-p53) and CAGE autoantibodies (anti-CAGE) was associated with an increased risk of reduced progression-free survival (PFS). In the multivariate analysis, anti-p53 remained significantly associated with shorter PFS, while anti-CAGE was not correlated with poor prognosis. The significant association between anti-p53 and worse PFS persisted after adjusting for gender, age, smoking status, pathological stage, and treatment. Kaplan–Meier survival analysis further confirmed that patients positive for anti-p53 had significantly shorter PFS ($P = 0.0025$).

Conclusion: Tumor-associated autoantibody anti-p53 correlates poor prognosis in lung adenocarcinoma patients, offering novel insights into tumor prognosis.

Keywords: lung adenocarcinoma, autoantibodies associated with lung cancer, prognosis, progression-free survival

Introduction

Lung cancer is the second most prevalent cancer worldwide and leads in both occurrence and fatality among all cancers in China.^{1,2} A major concern is that lung cancer is frequently diagnosed at advanced stages, which contributes to its high recurrence rate. Recent studies indicate that by 2020, lung adenocarcinoma had emerged as the predominant subtype of lung cancer worldwide. Specifically, among new lung cancer cases, adenocarcinoma accounted for 39% in male patients, surpassing squamous cell carcinoma (25%). In female patients, adenocarcinoma represented 57% of cases, whereas squamous cell carcinoma constituted only 12%.³ Despite its predominance, reliable biomarkers for predicting prognosis in lung adenocarcinoma remain scarce. Therefore, the identification of effective prognostic biomarkers for this disease is critically needed.

Tumor markers have long played a crucial role in cancer detection during its earliest stages.^{4–8} The detection of lung cancer has benefited from an array of blood biomarkers. Notably, both neuron-specific enolase (NSE) and cytokeratin fragment 21–1 (CYFRA 21–1) have shown significant associations with lung cancer.^{5,6} However, few biomarkers are currently available for monitoring lung cancer prognosis. Increased CYFRA 21–1 concentrations are associated with decreased overall survival in advanced-stage lung cancer.⁹ Additionally, a retrospective study demonstrated that high levels of carcinoembryonic antigen (CEA) both before and after surgery independently predict worse outcomes in stage I–III lung adenocarcinoma patients.¹⁰ However, the variety of available markers remains relatively limited.

During cancer’s initial development, the body’s immune defenses can detect trace amounts of irregular proteins produced by malignant cells—referred to as tumor-associated antigens (TAAs). These biological markers set off a targeted immunological reaction that prompts the generation of autoantibodies.¹¹ Studies have demonstrated that various types of cancer are associated with specific antibodies targeting TAAs. In lung cancer patients, gene mutations, translocations, or recombination occur early during tumor development. Upon release, these antigens trigger immune recognition, leading to antibody production—specifically tumor-associated autoantibodies (TAAs).^{12–14}

Although TAAs have been widely used in lung cancer screening, their potential role in prognosis monitoring remains underexplored. Some studies have suggested a possible association between TAAs and improved cancer outcomes,^{15,16} but the evidence remains inconclusive. This study aims to evaluate the prognostic value of TAAs in the peripheral blood of patients with lung adenocarcinoma.

Materials and Methods

Patients

This retrospective study included 161 lung adenocarcinoma patients from Henan Provincial People’s Hospital (2020–2022). Eligibility required participants to be ≥18 years old with biopsy-confirmed lung adenocarcinoma, as per the National Comprehensive Cancer Network guidelines.¹⁷ Participants were not included if they had simultaneous autoimmune disorders or additional primary cancers. Comprehensive patient data, covering gender, age, smoking history, cancer stage, and treatments, were systematically collected from the hospital information management system. Patients were monitored via phone. The follow-up deadline was December 2024 (Figure 1). All study participants provided informed consent. All procedures adhered to pertinent guidelines and laws. The Ethics Board at Henan Provincial People’s Hospital gave the study its consent (202390).

Serum Collection and Detection of Tumor-Associated Autoantibodies

Prior to TAAs detection, serum samples were centrifuged and subsequently stored at –80°C in a cryogenic freezer.

In this study, TAAs detection kits utilizing Enzyme-linked immunosorbent assay (ELISA) (Hangzhou Cancer Probe Biotech, Hangzhou, China). The kit number is CNDA-REG-20153402087. The results of the three batch test kits showed that all were no higher than 3.75 U/mL. Analyzing the specificity, the results showed that the influence of potential interfering substances and cross-reactive substances on the test kit was within ±20.0%. The results of the three batches of test kits showed a good linear relationship within the range of 3.75 to 60 U/mL, with $r \geq 0.9900$.

Principle of detection:

The kit contained a total of eight antigens, with streptavidin serving as the primary detecting antigen for background assessment, and the remaining antigens being TAAs: p53, GAGE7, PGP9.5, CAGE, MAGE A1, SOX2, GBU4-5. The seven antigen proteins were modified with streptomycin biotin and Myc tags for protein expression, purification, coating

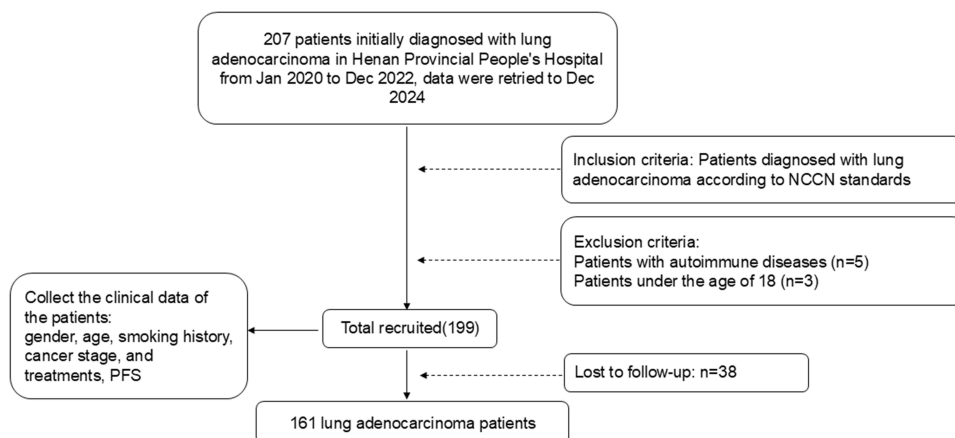


Figure 1 Flow diagram of the screening and enrollment of study patients.

and detection processes. Following purification, the antigens were indirectly coated onto the solid phase plate through a specific reaction between biotin and streptomycin, after which the diluted serum was applied. The TAAs present in the serum samples were specifically bound to the antigens on the solid phase plate. This led to the formation of an antigen-antibody-enzyme-labeled antibody complex. With any unbound enzyme-labeled anti-human IgG antibody being subsequently washed away. After reacting with a chromogenic substrate, the absorbance was measured at 450nm using a microplate reader, enabling the calculation of the relative concentration of TAAs.

Preparations:

① Before the experiment, all reagents were equilibrated to room temperature (18–25°C) and mixed. ② Wash working solution: 10 times of wash solution was diluted 10 times with pure water and prepared into wash working solution, which was stored at 2–8°C. ③ PBS buffer: pH 7.6. ④ Serum sample to be tested: 545 μ L of sample diluent was added to a 1.5mL EP tube, and then 5 μ L of the serum sample to be tested was added to the sample diluent and mixed. ⑤ Enzyme conjugate working Solution: “enzyme conjugate working solution” and “enzyme conjugate diluents” were mixed at a ratio of 1:19 to the desired volume of the experiment and prepared 15 min before use. ⑥ Chromogen: Mix “Chromogen A solution” and “Chromogen B solution” at a ratio of 1:19.

Experimental procedures:

① 200 μ L PBS buffer was added to each well, the plate was washed once and pat dry on clean absorbent paper. ② Add 50 μ L of quality control, calibrator, loading control and diluted samples to be tested in corresponding microwells, attach the sealing plate membrane and incubate at room temperature for 60 minutes with shaking. ③ Wash plate: shake off the liquid in the hole and pat dry on clean absorbent paper. Two hundred μ L of wash working solution was added to each well and then dried. Washing the plate was repeated 3 times and finally patted dry on clean absorbent paper. ④ 50 μ L of the diluted enzyme conjugate working solution was added to each well, shaken, affixed to the plate sealing membrane, and incubated for 30 minutes at room temperature with shaking. ⑤ Wash the plate: Repeat the above steps. ⑥ 100 μ L of the mixed chromogenic agent was added to each well and incubated at room temperature in the dark with shaking for 15 minutes. About 50 μ L of termination solution was added to each well and gently shaken. ⑦ OD values were read using a microplate reader within 30 minutes of the end of the reaction.

Statistical Analysis

This experiment is an exploratory study. Categorical data were summarized using counts and percentages [n (%)], whereas continuous measures were reported as means accompanied by standard deviations (mean \pm SD). The value of TAAs is expressed by the median (IQR). Tumors were staged based on the Union for International Cancer Control’s 8th edition TNM Malignant Tumors Classification,¹⁸ the lung cancer patients were categorized into four stages. To evaluate the influence of clinical factors on progression-free survival (PFS) in lung adenocarcinoma cases, we conducted Cox proportional hazards regression analyses. This study has verified the assumptions of the Cox proportional hazards model using the Schoenfeld residuals method, ensuring the reliability of the analysis results. The findings are presented as hazard ratios (HRs) along with their 95% confidence intervals (CIs).

Age was converted from continuous to binary, with 60 years as the cutoff to classify patients as elderly (\geq 60) or younger. Immunotherapy was defined as any regimen that used PD-1/PD-L1 inhibitor. “Other treatments” were treatment modalities that excluded surgical treatment or immunotherapy.

For assessing the link between TAAs and lung adenocarcinoma patient outcomes, both unadjusted and adjusted-for-multiple-factors analyses were conducted. The initial crude model did not account for any confounding variables. Subsequently, Model III incorporated adjustments for key factors, including patient demographics (gender, age), smoking history, tumor stage, and treatment protocols. The adjusted I model accounted for only two variables: gender and age. The adjusted II model expanded on this by also factoring in smoking status. The most comprehensive model (Model III) went a step further, incorporating not only demographic and lifestyle factors but also clinical variables such as pathological staging and treatment protocols for lung adenocarcinoma cases.

PFS was calculated as the time between initial disease diagnosis and the first observed disease progression. The Kaplan–Meier (K–M) method was employed to generate the PFS survival curve, with a cut-off for statistical relevance being a p-value below 0.05.

Results

Characterization of the Study Population

This retrospective study enrolled 161 patients with histologically confirmed lung adenocarcinoma, comprising 86 cases with disease progression and 75 progression-free individuals. Table 1 summarizes participant demographics and clinical features. The study included 161 participants, comprising 84 men (52.2%) and 77 women (47.8%), with an average age of 61.5 years (± 9.8 years). Sixty-five patients (40.4%) were smokers. For analytical purposes, pathological stages were dichotomized into early-stage (I & II; $n = 26$, 16.1%) and advanced-stage disease (III & IV; $n = 135$, 83.9%). Among the 161 patients, the most patients were treated with immunotherapy ($n = 93$, 57.8%).

Univariate Cox Regression Models of Seven TAAbs in Patients with Lung Adenocarcinoma

Table 2 presents HRs and 95% CIs for factors influencing disease progression in lung adenocarcinoma patients. We observed that female patients had an 41% depressed risk of disease progression compared to male patients ($P = 0.019$). The univariate analysis of seven lung cancer autoantibodies demonstrated a statistically significant association between anti-p53 levels and disease progression, with each unit increase corresponding to a 9% higher risk ($P < 0.001$). Mirroring this trend, the data in Table 2 indicated that elevated anti-CAGE levels similarly predicted poorer outcomes, showing a 5% increased risk per unit ($P = 0.039$). Notably, among the seven antibodies examined in lung adenocarcinoma cases, anti-p53 and anti-CAGE stood out as having distinct prognostic implications.

Table 1 Demographic and Clinical Characteristics of the Patients with Lung Adenocarcinoma

Variables	Total (n = 161)	No Progress (n = 75)	Progress (n = 86)	P Value
Gender, n (%)				0.01
Male	84 (52.2)	31 (41.3)	53 (61.6)	
Female	77 (47.8)	44 (58.7)	33 (38.4)	
Age, year, Mean \pm SD	61.5 \pm 9.8	60.3 \pm 10.2	62.6 \pm 9.3	0.15
Smoking status, n (%)				0.019
No	96 (59.6)	52 (69.3)	44 (51.2)	
Yes	65 (40.4)	23 (30.7)	42 (48.8)	
Pathological stage, n (%)				0.095
Phase I & II	26 (16.1)	16 (21.3)	10 (11.6)	
Phase III & IV	135 (83.9)	59 (78.7)	76 (88.4)	
Treatment, n (%)				< 0.001
Surgical treatment	11 (6.8)	9 (12)	2 (2.3)	
Immunotherapy	93 (57.8)	29 (38.7)	64 (74.4)	
Other treatments	57 (35.4)	37 (49.3)	20 (23.3)	
TAAbs, U/mL, Median(IQR)				
Anti-p53	0.7 (0.1, 2.1)	0.5 (0.1, 1.0)	0.9 (0.2, 3.0)	0.018
Anti-PGP9.5	0.3 (0.1, 1.0)	0.4 (0.1, 1.0)	0.2 (0.1, 1.0)	0.130
Anti-SOX2	0.7 (0.2, 2.1)	0.7 (0.1, 2.1)	0.6 (0.2, 1.8)	0.898
Anti-GAGE7	1.5 (0.7, 6.8)	1.3 (0.7, 5.8)	1.6 (0.7, 8.0)	0.472
Anti-GBU4.5	0.8 (0.2, 1.9)	0.6 (0.2, 1.9)	0.9 (0.3, 1.9)	0.501
Anti-MAGEA1	0.2 (0.1, 0.5)	0.2 (0.1, 0.4)	0.2 (0.1, 0.5)	0.138
Anti-CAGE	0.1 (0.1, 0.4)	0.1 (0.1, 0.3)	0.1 (0.1, 0.6)	0.350
PFS, Median(IQR)	19.0 (7.0, 28.0)	22.0 (19.0, 34.5)	10.0 (4.0, 21.8)	< 0.001

Abbreviations: SD, standard deviation; TAAbs, tumor-associated autoantibodies; IQR, Interquartile range; Anti-p53, p53 autoantibody; Anti-PGP9.5, PGP9.5 autoantibody; Anti-SOX2, SOX2 autoantibody; Anti-GAGE7, GAGE7 autoantibody; Anti-GBU4.5, GBU4.5 autoantibody; Anti-MAGEA1, MAGEA1 autoantibody; Anti-CAGE, CAGE autoantibody; PFS, progression-free survival. Notes: $P < 0.05$ indicated a statistically significant difference.

Table 2 Univariate Cox Regression Models for Patients with Lung Adenocarcinoma

Variables	HRs (95% CI)	P Value
Gender		
Male	Ref	
Female	0.59 (0.38,0.92)	0.019
Age, year	1.01 (0.99,1.04)	0.216
Smoking status		
No	Ref	
Yes	1.52 (1,2.33)	0.052
Pathological stage		
Phase I & II	Ref	
Phase III & IV	1.8 (0.92,3.51)	0.087
Treatment		
Surgical treatment	Ref	
Immunotherapy	3.29 (0.8,13.48)	0.097
Other treatments	1.38 (0.32,5.92)	0.666
Seven autoantibodies of lung cancer		
Anti-p53	1.09 (1.04,1.14)	< 0.001
Anti-PGP9.5	1.03 (0.95,1.13)	0.439
Anti-SOX2	1.03 (1,1.06)	0.061
Anti-GAGE7	0.9996 (0.989,1.0103)	0.945
Anti-GBU4.5	1.03 (0.98,1.08)	0.283
Anti-MAGEA1	1.02 (0.99,1.05)	0.129
Anti-CAGE	1.05 (1,1.09)	0.039

Abbreviations: Ref, reference; Anti-p53, p53 autoantibody; Anti-PGP9.5, PGP9.5 autoantibody; Anti-SOX2, SOX2 autoantibody; Anti-GAGE7, GAGE7 autoantibody; Anti-GBU4.5, GBU4.5 autoantibody; Anti-MAGEA1, MAGEA1 autoantibody; Anti-CAGE, CAGE autoantibody. Notes: Data presented are HRs and 95% CIs. $P < 0.05$ was considered statistically significant.

Multivariable Cox Regression Models of Anti-p53 in Patients with Lung Adenocarcinoma

The results of the univariate analysis indicated that anti-p53 had an impact on the progression of lung adenocarcinoma patients, with anti-p53 being considered a continuous variable. In the multivariate analysis and survival analysis, anti-p53 was categorized as a categorical variable, with cut-off values selected using X-tile software.^{19,20} The cut-off value of anti-p53 is 1.0 U/mL. Table 3 displayed the HRs and corresponding 95% CIs for anti-p53 and its association with disease progression in lung adenocarcinoma patients. In the unadjusted model, it was observed that patients with anti-p53 had an 91% increased risk of disease progression compared to patients without anti-p53 (95% CIs: 1.25, 2.93). After adjusted for gender and age, the HR was 1.88 (95% CIs: 1.22, 2.89, P for trend = 0.004). Model II, fine-tuned for gender, age, and smoking habits, exhibited a hazard ratio of 1.88. Finally, after adjusted for gender, age, smoking status, pathological staging and treatments, the HR was 1.91 (95% CIs: 1.23, 2.96, P for trend = 0.004).

Table 3 Multivariable Cox Regression Model for Anti-p53 in Patients with Lung Adenocarcinoma

Variables	N. event (%)	Crude HRs (95% CIs)	Adjusted I HRs (95% CIs)	Adjusted II HRs (95% CIs)	Adjusted III HRs (95% CIs)
Anti-p53	161				
Negative	106 (65.8)	Ref	Ref	Ref	Ref
Positive	55 (34.2)	1.91 (1.25~2.93)	1.88 (1.22~2.89)	1.88 (1.22~2.9)	1.91 (1.23~2.96)
P value		0.003	0.004	0.004	0.004

Abbreviations: Anti-p53, p53 autoantibody, anti-p53+: >1.0 U/mL; Ref, reference. Notes: Data presented are HRs and 95% CIs. Adjusted model I adjusted for gender and age. Adjusted model II adjusted for gender, age, smoking status. Adjusted model III adjusted for gender, age, smoking status, pathological staging and treatments. $P < 0.05$ was considered statistically significant.

Multivariable Cox Regression Models of Anti-CAGE in Patients with Lung Adenocarcinoma

Similar to anti-p53, anti-CAGE was treated as a categorical variable in multivariate analysis.^{19,20} The cut-off value of anti-CAGE is 10.1 U/mL. Table 4 showed the HRs and 95% CIs for anti-CAGE. In the unadjusted analysis, anti-CAGE-positive patients had a 2.66-fold higher disease progression risk compared to anti-CAGE-negative individuals (95% CIs: 1.15, 6.11, *P* for trend = 0.022). After adjusted for gender, age, smoking status, pathological staging and treatments, there was no significant difference between them. The HR was 2.07 (95% CIs: 0.88, 4.92, *P* for trend = 0.097).

Subgroup Analysis of Anti-p53 in Patients with Lung Adenocarcinoma

To explore whether the link between anti-p53 antibodies and patient outcomes in lung adenocarcinoma remained consistent across different groups, we conducted a stratified analysis. The subgroups were divided by gender, age, smoking history, disease stage, and treatment type (Table 5). This approach allowed us to assess the robustness of the observed associations under varying conditions.

Table 4 Multivariable Cox Regression Models for Anti-CAGE in Patients with Lung Adenocarcinoma

Variables	N. event (%)	Crude HRs (95% CIs)	Adjusted I HRs (95% CIs)	Adjusted II HRs (95% CIs)	Adjusted III HRs (95% CIs)
Anti-CAGE	161				
Negative	154 (95.7)	Ref	Ref	Ref	Ref
Positive	7 (4.3)	2.66 (1.15~6.11)	2.31 (1~5.36)	2.37 (1.01~5.56)	2.07 (0.88~4.92)
<i>P</i> value		0.022	0.051	0.048	0.097

Abbreviations: Anti-CAGE, CAGE autoantibody, anti-CAGE+: >10.1 U/mL; Ref, reference. Notes: Data presented are HRs and 95% CIs. Adjusted model I adjusted for gender and age. Adjusted model II adjusted for gender, age, smoking status. Adjusted model III adjusted for gender, age, smoking status, pathological staging and treatments. *P* < 0.05 was considered statistically significant.

Table 5 Anti-p53 Autoantibody Subgroup Analyses

Subgroup	Anti-p53		<i>P</i> Value	<i>P</i> for Interaction
	Negative	Positive		
Gender				0.509
Male	1(Ref)	1.99 (1.15~3.44)	0.014	
Female	1(Ref)	1.50 (0.72~3.13)	0.283	
Age				0.480
<60	1(Ref)	2.40 (1.15~4.99)	0.019	
≥60	1(Ref)	1.70 (0.99~2.91)	0.053	
Smoking				0.483
No	1(Ref)	1.62 (0.87~3.02)	0.125	
Yes	1(Ref)	2.05 (1.11~3.80)	0.022	
Pathological.stage, n (%)				0.924
Phase I & II	1(Ref)	1.86 (0.52~6.63)	0.340	
Phase III & IV	1(Ref)	1.84 (1.16~2.92)	0.009	
Treatment, n (%)				0.686
Surgical treatment	1(Ref)	300014527.68 (0~NE)	0.999	
Immunotherapy	1(Ref)	1.79 (1.08~2.96)	0.023	
Other treatments	1(Ref)	2.31 (0.92~5.83)	0.075	

Abbreviations: Anti-p53, p53 autoantibody, anti-p53+: >1.0 U/mL; Ref, reference; NE, not estimable. Notes: Age is a continuous variable, which is converted into a categorical variable. Pathological stage was grouped into two subgroups, eg, Phase I & II, and Phase III & IV, according to clinical value and the above-mentioned results. *P* < 0.05 was considered statistically significant.

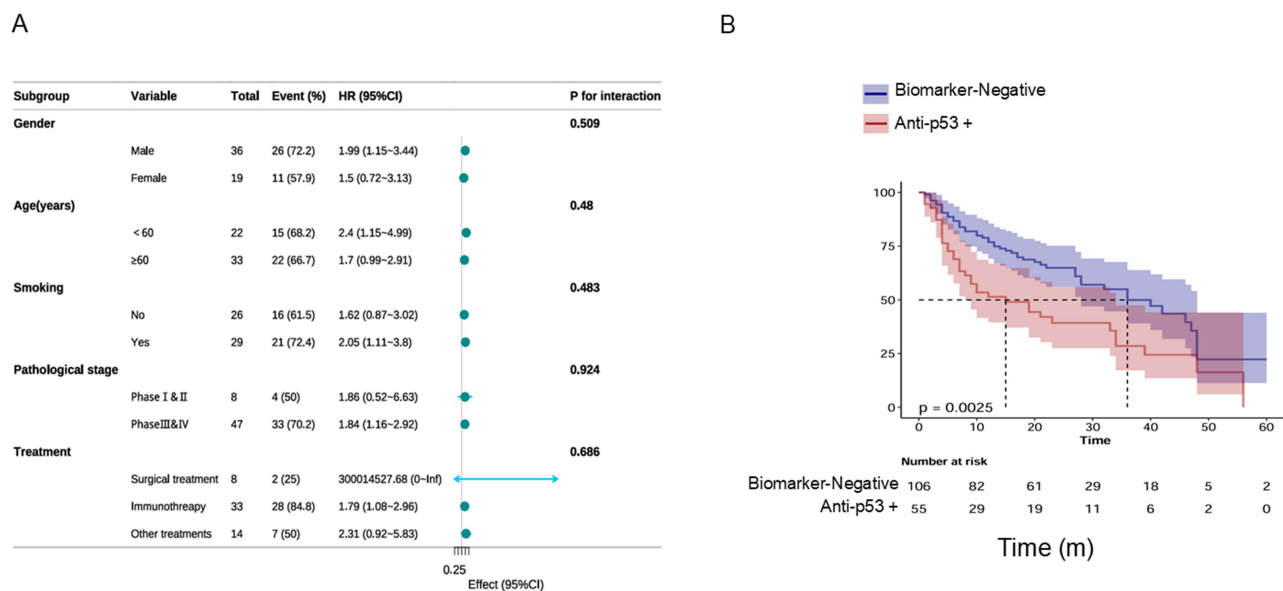


Figure 2 (A) The results of the forest plot for the anti-p53 subgroup analysis. **(B)** Progression-free survival analysis of anti-p53 in patients with lung adenocarcinoma. **Abbreviations:** Anti-p53, p53 autoantibody; *P* value < 0.05 indicated a statistically significant difference.

The study revealed that the relationship between anti-p53 and lung cancer patients' outcomes held steady across various demographics, including gender, age, smoking history, disease stage, and treatment. The interplay between these factors and the outcomes did not differ significantly. What's more, the association seemed stronger in males, the younger age group, smokers, and those with more advanced lung adenocarcinoma. Figure 2A showed the results of the forest plot for the anti-p53 subgroup analysis. Overall, the link between anti-p53 antibody and lung cancer outcomes remained consistent regardless of gender, age, smoking history, disease stage, or therapy.

Analysis of Survival

The associations between the presence of anti-p53 and PFS in lung adenocarcinoma patients were evaluated using K-M curves. The findings were depicted in Figure 2B. Specifically, Figure 2B demonstrated that patients positive for anti-p53 had significantly shorter PFS compare to those without anti-p53 ($P = 0.0025$). The presence of anti-p53 can predict the poor prognosis of patients.

Discussion

With the increasing incidence and mortality of lung cancer, there is a pressing need to identify reliable biomarkers for predicting tumor development and monitoring prognosis. In this study, we analyzed 161 patients with lung adenocarcinoma and detected the presence of seven TAAs. Our findings indicate that anti-p53 acts as an independent biomarker of poor prognosis, irrespective of gender, age, smoking status, pathological stage, or treatment modalities. Furthermore, patients positive for anti-p53 exhibited significantly shorter PFS.

As tumors develop and progress, they produce and release unique proteins known as TAAs. These TAAs arise from a variety of mechanisms, including protein overexpression, mutation, misfolding, and dysregulated degradation. The aberrant expression and presentation of these antigens can trigger a humoral immune response, stimulating the immune system to produce specific autoantibodies against TAAs, referred to as TAAs.²¹ This study evaluated a panel of seven tumor-associated autoantibodies (TAAs). Univariate analysis indicated that both anti-p53 and anti-CAGE were statistically significant in predicting the progression of lung adenocarcinoma. However, due to the limited number of anti-CAGE-positive patients, the results for this marker may be subject to potential bias. Furthermore, multivariate analysis showed that anti-CAGE was not statistically significant ($P > 0.05$) after adjustment for covariates. Therefore, we focused subsequent analyses exclusively on anti-p53.

The tumor suppressor gene product of p53 is one of the earliest discovered tumor suppressor genes and consists of 393 amino acids of transcription factors. Inactivation of p53 protein due to p53 gene mutation is a crucial step in the development of many cancers.^{22–24} Mutations in the p53 gene not only lead to the loss of its tumor-suppressor function but may also confer gain-of-function oncogenic properties. Concurrently, these alterations can induce the production of specific autoantibodies. For example, in pancreatic cancer, the p53R172H missense mutation modulates the expression of chemokines including CXCL1, contributing to an immunosuppressive tumor microenvironment and reducing the efficacy of immune checkpoint inhibitor therapy.²⁵ Furthermore, p53 mutants often have a longer half-life, resulting in their abnormal accumulation within tumor cells. This accumulation is not only associated with the malignant progression of the tumor but may also trigger the body's immune system to produce specific autoantibodies.

Numerous studies in recent years have established the significant value of anti-p53 in the early detection of various cancer types. In lung cancer, anti-p53 have been incorporated into clinical screening strategies. Detection of anti-p53 via ELISA, particularly in combination with other tumor-associated antibodies, has been shown to significantly improve the early diagnosis rate of lung cancer. Apart from its value in early cancer screening, the anti-p53 also demonstrates great potential in cancer prognosis assessment. A study investigated the impact of two combined methods anti-p53 expression and preoperative serum carcinoembryonic antigen (S-CEA) testing on the prognosis of colorectal cancer patients. The results showed that the combined method of p53 and S-CEA detection was more effective in evaluating the prognosis of colorectal cancer compared to the traditional combination.²⁶ A recent investigation of a panel of tumor-associated autoantibodies, including anti-p53, anti-CAGE, anti-MAGEA4, anti-GAGE7, anti-UTP14A, anti-IMP2 and anti-PSMC1 7, revealed that patients with these TAAbs exhibited a longer PFS.¹⁵ Additionally, another study reported that a panel of five TAAbs targeting anti-p53, anti-BRCA2, anti-HUD, anti-TRIM21, and anti-NY-ESO-1 was linked to a better prognosis and extended PFS.¹⁶ The research on non-small cell lung cancer patients linked elevated anti-PGP9.5 and anti-p53 levels to reduced PFS.²⁷ Moreover, an earlier study indicated that the survival rate of TAAbs-positive lung cancer patients was significantly lower compare to negative or low-titer patients at 30-month mark.²⁸ The prognostic value of anti-p53 is closely linked to p53 mutation and functional disruption.^{29,30} Another research showed that loss of p53 function leads to upregulation of IL-34 gene normally suppressed by p53. This enhances CD36-mediated fatty acid oxidation, promotes M2-type polarization of foam-like tumor-associated macrophages (TAMs), and inhibits CD8+ T cell function, ultimately facilitating immune escape. Importantly, blocking the IL-34-CD36 axis can restore anti-tumor immunity and synergize with anti-PD-1 treatment.³¹ This might partly explain the reason why patients with positive p53 autoantibodies have a poorer prognosis.

TAAbs have emerged as promising biomarkers for monitoring lung cancer prognosis, offering several practical advantages. Firstly, TAAbs are more readily detectable than their corresponding TAAs. Secondly, they demonstrate high stability under routine sample handling and storage conditions, with low pre-analytical requirements and an extended serum half-life. Thirdly, serum-based TAAbs detection-commonly performed via ELISA-is minimally invasive, technically feasible, and highly reproducible. Moreover, TAAbs can often be detected months or even years before radiographic signs become apparent.

However, several limitations must be considered when using TAAbs for prognostic prediction. Firstly, we acknowledge the shortcomings of our study. The study was a single-center study with a small sample size. Secondly, we have only explored the value of TAABS in the prognosis of lung cancer. Further research is needed for other cancer types. Clinically, TAAbs currently have limited application in routine practice. The positive results may not be exclusive to lung cancer, as these antibodies can occur in other benign or malignant conditions. In the future, we will need more experiments to continue exploring.

Conclusion

In summary, this study found that patients with the anti-p53 exhibited shorter PFS. This finding holds significant clinical implications, offering new insights and methods for monitoring the prognosis of lung adenocarcinoma patients. However, the role of the immune response in lung adenocarcinoma patients remains not fully understood. In the future, we will conduct more large-scale and multi-center studies to further explore the mechanisms and effects involved, providing more valuable reference evidence for clinical significance.

Abbreviations

TAAbs, tumor associated-autoantibodies; ELISA, Enzyme-linked immunosorbent assay; anti-p53, p53 autoantibodies; anti-CAGE, CAGE autoantibodies; PFS, progression-free survival; CTCs, circulating tumor cells; ctDNA, circulating tumor DNA; TEPs, tumor educated platelets; NSE, neuron-specific enolase; CYFRA 21-1, cytokeratin fragment 21-1; OS, overall survival; CEA, carcinoembryonic antigen; TAAs, tumor-associated antigens; HRs, hazard ratios; CIs, confidence intervals; K-M, Kaplan-Meier; AUC, area under curve; NSFC, Natural Science Foundation of China.

Data Sharing Statement

All the results are presented in the article. Further inquiries can be directed to the corresponding authors.

Ethics Statement

The study received ethical clearance from Henan Provincial People's Hospital. (Approval number. 202390). All experiments and procedures were performed according to the Declaration of Helsinki (as revised in 2013).

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.

Funding

This study was supported by the National Natural Science Foundation of China (NSFC) (82002210) and the Henan Provincial medical science and technology research project (LHGJ20240098).

Disclosure

The authors report no conflicts of interest in this work.

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