



# Safety and efficacy of immune checkpoint inhibitors in non-small cell lung cancer patients with preexisting antinuclear antibodies: a retrospective cohort study

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**Background:** Antinuclear antibodies (ANAs) predicting the safety and efficacy of patients with advanced non-small cell lung cancer (NSCLC) treated with immune checkpoint inhibitors (ICIs) are still a matter of debate considering previous studies showed quite different results based on different ANA cut-off values. Thus, we investigated the associations between different ANA titers and the safety and efficacy of ICIs. Moreover, we also briefly discussed the effects of anti-thyroglobulin (ATG) and anti-thyroid peroxidase (ATPO) on the safety of ICIs.

**Methods:** A total of 159 Chinese patients confirmed to have locally-advanced or metastatic NSCLC given ICIs or chemoimmunotherapy in Peking Union Medical College Hospital from January 2015 to December 2020 were analyzed retrospectively and were followed up until December 2020 or death or loss to follow-up. Patients' characteristics were retrieved from medical records. ANAs were detected by the indirect immunofluorescence assay, ATG and ATPO by the electrochemiluminescence immunoassay. The severity of immune-related adverse events (irAEs) was graded according to the Common Terminology Criteria for Adverse Events (CTCAE 5.0) and the efficacy was evaluated by the Response Evaluation Criteria in Solid Tumors (RECIST 1.1).

**Results:** The incidence of irAEs, median progression-free survival (mPFS) of the ANA negative and positive groups were 26.0% vs. 31.4% (P=0.457), 17.7 vs. 10 months (P=0.603) for the cut-off value of 1:80; 26.2% vs. 33.9% (P=0.305), 11.9 vs. 10.6 months (P=0.957) for 1:160; and 25.9% vs. 45.8% (P=0.047), and 11.9 vs. 7.7 months (P=0.471) for 1:320, separately. Besides, ANA titer  $\geq 1:320$  was associated with irAEs [odds ratio (OR) =4.9, 95% confidence interval (CI): 1.45–16.52, P=0.01] and the incidence of adverse skin reactions differed greatly between the negative and positive groups (9.7% vs. 32%, P=0.003). Moreover, a total of 52 out of 159 patients were tested for ATG and ATPO. 46 patients were negative and 6 were positive, with the incidence of abnormal thyroid function being 4.3% vs. 50% (P=0.005), respectively.

**Conclusions:** Preexisting ANAs may not correlate with the clinical benefit of immunotherapy in patients with NSCLC but may be associated with adverse skin reactions. Besides, ATG or ATPO has the potential to

predict thyroid dysfunction.

**Keywords:** Immune-related adverse events (irAEs); immune checkpoint inhibitors (ICIs); antinuclear antibodies (ANAs); safety; efficacy

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## Introduction

Lung cancer, causing an estimated 1.6 million deaths each year, is the most common cause of cancer death globally (1,2). According to the histological type, lung cancer can be divided into non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Adenocarcinoma comprises approximately 40–50% of NSCLC, and squamous cell carcinoma comprises 20–30%. In recent years, immunotherapy has brought new hope to patients with lung cancer (3–8). Immune checkpoint inhibitors (ICIs), monoclonal antibodies that bind to programmed cell death-1 (PD-1)/programmed death ligand-1 (PD-L1) and cytotoxic T-lymphocyte antigen 4 (CTLA-4), can boost anti-tumor immunity by blocking T-cell inhibition. However, an exaggerated T-cell response against normal tissues could generate high levels of proinflammatory cytokines, leading to unique toxicities named immune-related adverse events (irAEs).

Several potential risk factors for the development of irAEs from ICIs have been suggested, including interleukin (IL)-17, eosinophil counts, absolute lymphocyte count, preexisting autoimmune diseases (AIDs), and so on (9–14). Furthermore, previous studies indicated that preexisting anti-thyroglobulin (ATG) and anti-thyroid peroxidase (ATPO) were more common among patients receiving ICIs who subsequently developed thyroid dysfunction (15,16). Besides, Biomarkers including PD-L1 expression, density of tumor infiltrating lymphocyte (TIL), tumor mutational burden (TMB), and mismatch-repair (MMR) deficiency, gut microbiota, circulating biomarkers, and patient previous history are regarded as being associated with efficacy of ICIs (17,18). Moreover, some researchers also attempted to discover the relationship between antinuclear antibodies (ANAs) and the safety and efficacy of ICIs but acquired different results (15,19–21).

ANAs, which identify nuclear macromolecules and their complexes, are a diverse group of autoantibodies (22,23). It is generally believed that ANAs are associated with various

systemic rheumatic diseases, including systemic lupus erythematosus (SLE) and systemic sclerosis (SSc), among others. However, ANAs are also present in a substantial proportion of healthy individuals, where they have been associated with demographic factors such as older age, female sex, and parity, among others (24). A previous study has shown that based on different cut-off values of serum dilution titer, the proportion of positive ANAs in the healthy population is quite different, including 31.7% at 1:40, 13.3% at 1:80, 5.0% at 1:160, and 3.3% at 1:320 (25).

Considering that individuals with positive ANAs might present susceptibility to AIDs which might compromise safety but boost efficacy of ICIs, it is reasonable to speculate that immunotherapy in NSCLC patients with positive ANAs may demonstrate different safety profiles and efficacy. However, clinical trial data on ICIs in these patients are not only sparse but also different from different studies (15,19–21). Moreover, the cut-off value of positive ANA titer varied among studies. Herein, our research investigates the safety and efficacy of ICIs in locally-advanced or metastatic NSCLC patients according to different ANA titers and briefly discusses the effects of ATG and ATPO on the safety of ICIs, in hopes of providing more information for the predictive biomarkers of ICIs. We present the following article in accordance with the STROBE reporting checklist (available at <https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-464/rc>).

## Methods

### Patients

This cohort study was conducted retrospectively. Patients eligible for inclusion were collected under the following criteria: (I) All patients were confirmed to have NSCLC by a pathology assessment in Peking Union Medical College Hospital from January 1, 2015 to December 31, 2020; (II) TNM stages of tumors were III–IV; (III) All patients received ICIs (PD-1 or PD-L1 or CTLA-4 inhibition with

or without chemotherapy). (IV) Peripheral blood samples were collected before the initiation of immunotherapy. The exclusion criteria included the followings: (I) patients suffering from any symptomatic autoimmune diseases; (II) critical medical records and imaging data were not available; (III) peripheral blood samples were not qualified for testing ANAs. Finally, 159 Chinese patients were included in our study. Patients were followed up every 2 months until December 31, 2020 or death or loss to follow-up and the number of follow-up times could be increased whenever they had new complaints of discomfort.

### **Data collection**

The patients' characteristics such as age, gender, Eastern Cooperative Oncology Group (ECOG) performance status score, smoking history, pathology, stage, coexisting driver gene mutations, treatment lines, and treatment strategies were retrieved from medical records. Missing values regarding characteristics and tumor response were ignored.

### **Evaluation of safety**

The severity of irAEs was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) 5.0.

### **Evaluation of efficacy**

According to the solid tumor efficacy evaluation standard [Response Evaluation Criteria in Solid Tumors (RECIST 1.1)], the evaluation grade was divided into complete remission (complete response, CR), partial remission (partial response, PR), stable (stable disease, SD), and disease progression (progressive disease, PD). The objective response rate (ORR) was defined as the proportion of patients whose tumors shrunk to a certain amount and maintained for a certain period of time, and included the proportion of CR and PR. The disease control rate (DCR) was defined as the overall proportion of patients with remission or in a stable condition after treatment, including the proportion of CR, PR, and SD. Progression-free survival (PFS) and overall survival (OS) were defined as the time from the beginning of immunotherapy to tumor progression (PFS) or death (OS) from any cause.

### **Measurement of ANAs, ATG and ATPO**

Blood samples were collected before the initiation of

immunotherapy and archival samples were allowed. ANAs were detected by the indirect immunofluorescence assay, and the detection reagent which used Hep-2 cells and monkey liver as the antigen matrix was provided by EUROIMMUN Medizinische Labordiagnostika AG (Germany). ANA titer  $\geq 1:80$  is commonly regarded as positive. In our study, in order to explore the effect of different ANA titers on the efficacy and safety of immunotherapy, we used 1:80, 1:160, and 1:320 as the cut-off values for negative (less than the cut-off value) or positive (greater than or equal to the cut-off value) ANA. ATG and ATPO were measured by the electrochemiluminescence immunoassay, ECLIA (Cobas; Roche, Basel, Switzerland). The reference intervals were 0 to 115 IU/mL for ATG and 0 to 34 IU/mL for ATPO.

### **Statistical analysis**

All data were analyzed and processed by SPSS 22.0. The  $\chi^2$  test or Fisher's exact test was used to compare categorical variables. Student's t and Kruskal-Wallis H tests were used to compare continuous variables. Survival outcomes were estimated with the Kaplan-Meier method and compared between groups using the log-rank test. For multivariate analysis, logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs). All statistical tests were two-sided, and  $P < 0.05$  indicated a statistical difference. Figures were created with GraphPad Prism (San Diego, CA, USA).

### **Ethical approval**

This study was performed in accordance with the principles for Good Clinical Practice and the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Peking Union Medical College Hospital on September 1, 2021 (No. S-K1744) and individual consent for this retrospective analysis was waived.

## **Results**

### **Baseline characteristics**

A total of 159 NSCLC patients treated with ICIs were enrolled in this study. The baseline characteristics are shown in *Table 1*. Whether 1:80, 1:160, or 1:320 were used as the cut-off values, baseline characteristics including age, gender, ECOG performance status score, smoking history, pathology, stage, coexisting driver gene mutations, treatment lines and strategies showed no significant

**Table 1** Baseline characteristics

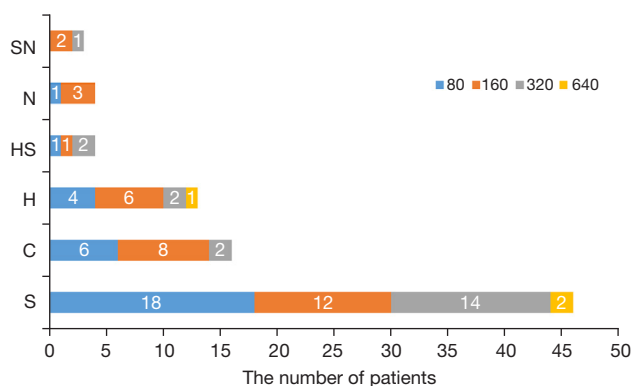
Characteristics	ANA <1:80 (N=73)	ANA ≥1:80 (N=86)	P	ANA <1:160 (N=103)	ANA ≥1:160 (N=56)	P	ANA <1:320 (N=135)	ANA ≥1:320 (N=24)	P
Age			0.484			0.889			0.242
≤60 years	25 (34.2%)	25 (29.2%)		32 (31.1%)	18 (32.1%)		40 (29.6%)	10 (41.7%)	
>60 years	48 (65.8%)	61 (70.9%)		71 (68.9%)	38 (67.9%)		95 (70.4%)	14 (58.3%)	
Gender			0.864			0.324			0.442
Male	51 (69.9%)	59 (68.6%)		74 (71.8%)	36 (64.3%)		95 (70.4%)	15 (62.5%)	
Female	22 (30.1%)	27 (31.4%)		29 (28.2%)	20 (35.7%)		40 (29.6%)	9 (37.5%)	
ECOG performance status			0.591			1.000			0.235
0–1	67 (91.8%)	79 (95.2%)		95 (93.1%)	51 (94.4%)		125 (94.0%)	21 (91.3%)	
≥2	6 (8.2%)	4 (4.8%)		7 (6.9%)	3 (5.6%)		8 (6.0%)	2 (8.8%)	
Smoking history			0.632			0.544			0.656
No	27 (37.0%)	28 (33.3%)		34 (33.3%)	21 (38.2%)		46 (34.3%)	9 (39.1%)	
Yes	46 (63.0%)	56 (66.7%)		68 (66.7%)	34 (61.8%)		88 (66.7%)	14 (60.9%)	
Pathology			0.437			0.166			0.581
Adenocarcinoma	44 (60.3%)	47 (54.7%)		58 (56.3%)	33 (58.9%)		78 (57.8%)	13 (54.2%)	
Squamous cell carcinoma	25 (34.2%)	35 (40.7%)		40 (38.8%)	20 (35.7%)		49 (36.3%)	11 (45.8%)	
Adenosquamous carcinoma	1 (1.4%)	3 (3.5%)		1 (1.0%)	3 (5.4%)		4 (3.0%)	0	
Large cell carcinoma	3 (4.1%)	1 (1.2%)		4 (3.9%)	0		4 (3.0%)	0	
Stage			0.260			0.182			0.493
III	19 (26.0%)	16 (18.6%)		26 (25.2%)	9 (16.1%)		31 (23.0%)	4 (16.7%)	
IV	54 (74.0%)	70 (81.4%)		77 (74.8%)	47 (83.9%)		104 (77.0%)	20 (83.3%)	
Driver gene mutations			0.742			0.602			0.266
Positive									
<i>EGFR</i>	19 (26.0%)	18 (20.9%)		25 (24.3%)	12 (21.4%)		30 (22.2%)	7 (29.2%)	
<i>KRAS</i>	6 (8.2%)	5 (5.8%)		9 (8.7%)	2 (3.6%)		11 (8.1%)	0	
<i>ROS-1</i>	4 (5.5%)	4 (4.7%)		5 (4.9%)	3 (5.4%)		8 (5.9%)	0	
Negative	44 (60.3%)	61 (70.9%)		64 (62.1%)	39 (69.6%)		86 (63.7%)	17 (70.8%)	
Treatment lines			0.395			0.983			0.726
First line	32 (43.8%)	45 (52.3%)		49 (47.6%)	28 (50.0%)		66 (48.9%)	11 (45.8%)	
Second line	22 (30.1%)	27 (31.4%)		32 (31.1%)	17 (30.4%)		43 (31.9%)	6 (25.0%)	
Third line	12 (16.4%)	7 (8.1%)		13 (12.6%)	6 (10.7%)		15 (11.1%)	4 (16.7%)	
≥ Fourth line	7 (9.6%)	7 (8.1%)		9 (8.7%)	5 (8.9%)		11 (8.1%)	3 (12.5%)	

**Table 1** (continued)

Table 1 (continued)

Characteristics	ANA <1:80 (N=73)	ANA ≥1:80 (N=86)	P	ANA <1:160 (N=103)	ANA ≥1:160 (N=56)	P	ANA <1:320 (N=135)	ANA (≥1:320) (N=24)	P
Treatment received			0.763			0.413			0.354
ICI monotherapy [anti-PD-(L)-1]	25 (34.2%)	33 (38.4%)		36 (35.0%)	22 (39.3%)		47 (34.8%)	11 (45.8%)	
Combined immunotherapy [anti- PD-(L)1 & anti-CTLA4]	1 (1.4%)	2 (2.3%)		1 (1.0%)	2 (3.6%)		2 (1.5%)	1 (4.2%)	
Chemoimmunotherapy*	47 (64.4%)	51 (59.3%)		66 (64.1%)	32 (57.1%)		86 (63.7%)	12 (50.0%)	
Median duration of ICIs, months	6.5	6.7	0.946	6.3	7.5	0.386	6.5	6.6	0.817

\*, chemoimmunotherapy means immunotherapy [anti-PD-(L)1 ± anti-CTLA4] combined with chemotherapy (platinum doublet or single drug chemotherapy including paclitaxel, docetaxel, pemetrexed and gemcitabine). ANA, antinuclear antibodies; ECOG, Eastern Cooperative Oncology Group; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; CTLA-4, cytotoxic T-lymphocyte antigen 4; ICI, immune checkpoint inhibitor.



**Figure 1** The distribution of ANA karyotypes. ANA, antinuclear antibody; S, speckled type; C, cytoplasmic type; H, homogeneous type; SN, speckled-nucleolar type; HS, homogeneous-speckled type; N, nucleolar type.

differences between the negative and positive groups.

The positive rate of ANA in patients with NSCLC when using 1:80 as the cut-off value was 54.1%, significantly higher than 13.3% in healthy controls (25). As shown in *Figure 1*, the staining pattern included speckled type (S, 53.5%), cytoplasmic type (C, 18.6%), homogeneous type (H, 15.1%), homogeneous-speckled type (HS, 4.7%), nucleolar type (N, 4.7%), and speckled-nucleolar type (SN, 3.5%).

### Safety and efficacy

A total of 28.9% (46/159) of the patients developed 64

irAEs, and 5.7% (9/159) developed 11 grade 3–5 irAEs (*Table 2*). These adverse reactions manifested as pruritus, rash, scalp ulcer, hypothyroidism, hyperthyroidism, elevated alanine aminotransferase, hepatitis, interstitial pneumonia, renal failure, and nephrotic syndrome, among others. Most adverse reactions were mild, without the need for glucocorticoids and ICI treatment interruption.

The median follow-up time was 12.2 months (95% CI: 10.5 to 13.9). Among the 46 patients who suffered from irAEs, 19 (26.0%) patients in the negative group (ANA <1:80) and 27 (31.4%) in the positive group (ANA ≥1:80) developed irAEs (P=0.457). Similarly, when using 1:160 as the cut-off value, the incidence of irAEs was 26.2% vs. 33.9% (P=0.305) in both groups. However, with the cut-off value of 1:320, the incidence of irAEs in the negative (ANA titer <1:320) and positive (ANA titer ≥1:320) groups was 25.9% vs. 45.8% (P=0.047). In multivariate models (*Table 3*), ANA titer ≥1:320 was also associated with irAEs (OR =4.9, 95% CI: 1.45–16.52, P=0.01). Further analysis showed a significant difference in the incidence of adverse skin reactions between the 2 groups (9.7% vs. 32%, P=0.003). Adverse reactions involving other systems, such as the thyroid, liver, heart, lung, and kidney, showed no significant differences between the 2 groups (*Figure 2*), and no significant differences were observed regarding grade 3/4 irAEs.

The ORR and DCR of the ANA negative and positive groups with the cut-off value of 1:80 were 37.1% vs. 43.9% (P=0.398) and 88.6% vs. 82.9% (P=0.324), respectively.

**Table 2** Distribution of irAEs

Adverse events	N (%) <sup>*</sup>	Grade $\geq 3$ irAEs, N
Cutaneous	21 (32.8)	
Rash	18 (28.1)	3
Pruritus	2 (3.1)	
Scalp ulcer	1 (1.6)	
Endocrine disorders	20 (31.3)	
Hypothyroidism	9 (14.1)	
Hyperthyroidism	8 (12.5)	
Hypophysitis	1 (1.6)	1
Adrenocortical dysfunction	1 (1.6)	
Hyperglycemia	1 (1.6)	
Gastrointestinal	10 (15.6)	
Alanine aminotransferase/ bilirubin increase	8 (12.5)	1
Pancreatitis or lipase/amylase increase	2 (3.1)	1
Cardiovascular	5 (7.8)	
Myocarditis/cardiac troponin I increase	4 (6.3)	
Heart failure	1 (1.6)	1
Pneumonitis	4 (6.3)	1
Renal	2 (3.1)	
Elevated creatinine	1 (1.6)	
Membranous nephropathy	1 (1.6)	1
Fever	1 (1.6)	
Nervous system	1 (1.6)	

<sup>\*</sup>, total =64 events in 46 patients. irAEs, immune-related adverse events.

As shown in the Kaplan-Meier curves of PFS (*Figure 3*), the median progression-free survival (mPFS) was 17.7 vs. 10 months ( $P=0.603$ ). When using 1:160 as the cut-off value, the ORR, DCR and mPFS of the ANA negative and positive groups were 35.7% vs. 50.0% ( $P=0.086$ ), 87.8% vs. 81.5% ( $P=0.293$ ), 11.9 vs. 10.6 months ( $P=0.957$ ) respectively (*Figure 4*). What is more, the ORR, DCR and mPFS of the ANA negative (ANA <1:320) and positive groups (ANA  $\geq 1:320$ ) were 40.3% vs. 43.5% ( $P=0.450$ ), 87.6% vs. 73.9% ( $P=0.086$ ) and 11.9 vs. 7.7 months ( $P=0.471$ ), respectively (*Figure 5*).

Moreover, 52 out of 159 patients were tested for ATG and ATPO. Of these, 46 (88.5%) patients were negative and 6 (11.5%) were positive. A total of 34.6% (18/52) of the patients developed 27 irAEs, mainly including 8 skin adverse events (rash: 7; pruritus: 1), 5 thyroid dysfunction (hypothyroidism: 3, hyperthyroidism: 2), 4 liver adverse events (elevated alanine aminotransferase), 2 pulmonary adverse events (interstitial pneumonia) and 2 renal adverse events (nephrotic syndrome: 1; elevated serum creatinine: 1) and some more scarce ones. 7.7% (4/52) of patients developed 6 grade 3–5 irAEs. Because of limited data, further analysis was carried out on 3 mostly affected systems. As shown in *Figure 6*, the incidence of thyroid dysfunction was 4.3% vs. 50% ( $P=0.005$ ) between the negative and positive groups. Adverse reactions involving the skin and liver showed no significant differences.

## Discussion

The introduction of ICIs into the treatment of NSCLC has transformed the therapeutic landscape. A large number of studies have shown that the application of immunotherapy for specific NSCLC patients can produce profound benefits (26–29). However, patients with preexisting AIDs are typically excluded from clinical trials of ICIs given concerns of exacerbating the underlying AIDs and leading to irAEs. Immune-related toxicities include the more commonly seen events such as hypothyroidism or skin rash and the more scarce and severe diseases like colitis, pneumonitis, autoimmune hepatitis, and encephalitis (30–34). A total of 7–13% of NSCLC patients treated with PD-1 inhibitors experienced grade 3 or higher toxicities, and up to 2% of patients receiving ICIs have died from therapy-related toxicities (35–38). Fortunately, corticosteroids and immunosuppressants can manage most irAEs successfully. Most adverse reactions in our study were mild, without the need to stop ICIs and initiate corticosteroids and immunosuppressants.

Some researchers in recent years have been exploring the influence of preexisting AIDs on immunotherapy. In a study that enrolled 751 patients who suffered from malignant tumors and received ICI monotherapy, 85 patients (11.3%) had preexisting AIDs, including clinically active state (17.6%) and inactive state (82.4%) (39). Among the patients with preexisting AIDs, the incidence of irAEs of any grade was significantly higher than those without AIDs (65.9% vs. 39.9%,  $P<0.0001$ ). However, no significant differences were observed regarding grade 3/4 irAEs. Regarding ORR,

**Table 3** Univariate and stepwise multivariate analysis of risk factors for any grade of irAEs

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P	OR (95% CI)	P
Age				
≤60 years	1 (reference)		1 (reference)	
>60 years	0.61 (0.3–1.26)	0.18	0.79 (0.35–1.77)	0.56
Gender				
Male	1 (reference)		1 (reference)	
Female	0.98 (0.46–2.05)	0.95		
ECOG performance status				
0–1	1 (reference)		1.63 (0.49–5.44)	0.42
≥2	0.25 (0.03–2.03)	0.19	0.17 (0.02–1.67)	0.13
Smoking history				
No	1 (reference)		1 (reference)	
Yes	1.02 (0.49–2.09)	0.97	0.96 (0.3–3.02)	0.94
Pathology				
Adenocarcinoma	1 (reference)		1 (reference)	
Squamous cell carcinoma	1.15 (0.56–2.37)	0.71	0.87 (0.33–2.3)	0.77
Adenosquamous carcinoma	2.83 (0.37–21.55)	0.31	0.81 (0.06–10.17)	0.87
Large cell carcinoma	0.72 (0.07–7.99)	0.79	3.96 (0.35–44.21)	0.26
Stage				
III	1 (reference)		1 (reference)	
IV	0.72 (0.32–1.61)	0.43	0.72 (0.27–1.89)	0.50
Driver gene mutations				
Negative	1 (reference)		1 (reference)	
Positive	0.80 (0.38–1.67)	0.55	0.74 (0.23–2.46)	0.63
Treatment lines				
First line	1 (reference)		1 (reference)	
Second line	0.78 (0.36–1.71)	0.54	1.29 (0.38–4.4)	0.68
Third line	0.37 (0.1–1.38)	0.14	0.41 (0.08–2.13)	0.29
≥ Fourth line	0.53 (0.14–2.09)	0.37	1 (0.15–6.52)	1.00
Treatment received				
ICI monotherapy [anti-PD-(L)-1]	1 (reference)		1 (reference)	
Combined immunotherapy [anti-PD-(L)1 & anti-CTLA4]	1.93 (0.14–25.95)	0.62	1.45 (0.06–32.97)	0.82
Chemoimmunotherapy*	1.50 (0.71–3.16)	0.29	1.51 (0.48–4.79)	0.49

**Table 3** (continued)

Table 3 (continued)

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P	OR (95% CI)	P
ANA titers				
<1:320	1 (reference)		1 (reference)	
≥1:320	2.42 (0.99–5.89)	0.05	4.9 (1.45–16.52)	0.01
ANA karyotypes				
None	1 (reference)		1 (reference)	
S	1.20 (0.53–2.72)	0.67	0.78 (0.28–2.17)	0.64
C	1.64 (0.52–5.14)	0.39	0.9 (0.25–3.31)	0.88
H	0.50 (0.10–2.45)	0.39	0.22 (0.03–1.39)	0.11
SN	0 (0–0)	1.00	0	1.00
HS	2.74 (0.36–20.82)	0.33	1 (0.09–11.17)	1.00
N	8.21 (0.8–83.83)	0.08	7 (0.6–81.77)	0.12

\*, chemoimmunotherapy means immunotherapy [anti-PD-(L)1 ± anti-CTLA4] combined with chemotherapy (platinum doublet or single drug chemotherapy including paclitaxel, docetaxel, pemetrexed and gemcitabine). irAEs, immune-related adverse events; ECOG, Eastern Cooperative Oncology Group; ICI, immune checkpoint inhibitor; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; ANA, antinuclear antibody; S, speckled type; C, cytoplasmic type; H, homogeneous type; SN, speckled-nucleolar type; HS, homogeneous-speckled type; N, nucleolar type; OR, odds ratio; CI, confidence interval.

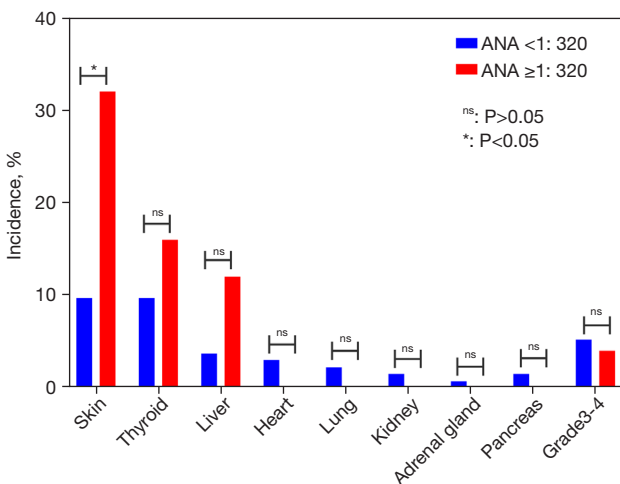


Figure 2 Incidence of irAEs of any grade between patients with ANA titer <1:320 or ≥1:320. IrAEs, immune-related adverse events; ANA, antinuclear antibody; ns, not significant.

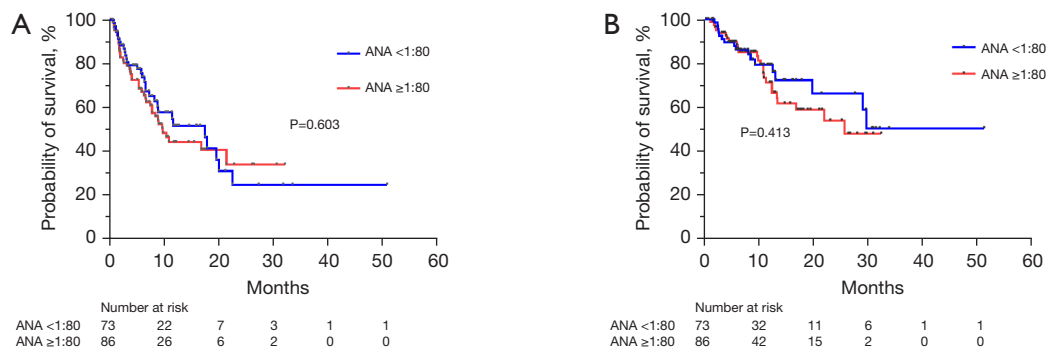
PFS, and OS, there were also no significant differences between the 2 groups. In a single-arm international study named SAUL (NCT02928406), 997 patients were enrolled and received atezolizumab, among which 35 patients had AIDs at baseline. Median OS was 8.2 months (95% CI: 6.5–

11.7 months) and 8.8 months (95% CI: 7.6–9.9 months) in patients with or without pre-existing AIDs, respectively, which meant efficacy was similar between 2 groups (40). These findings indicate that AIDs have no significant effects on the effectiveness of immunotherapy, but will compromise safety (40-43). However, more data is needed in this population.

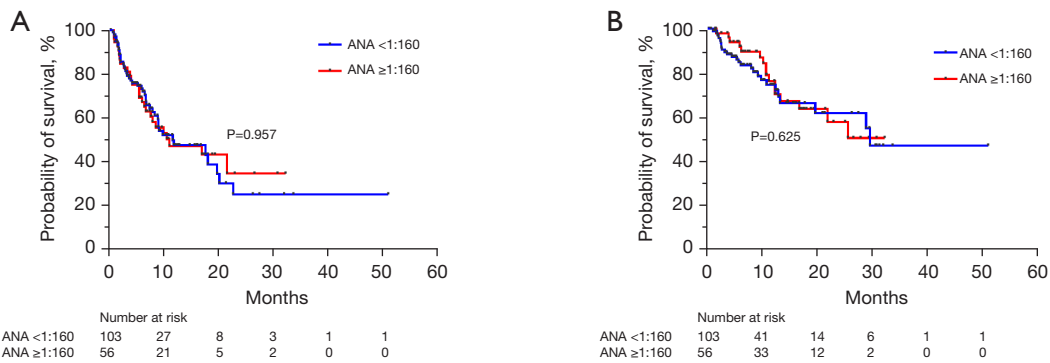
ANAs, observed in patients with a wide range of AIDs, are regarded as critical biomarkers when assessing systemic rheumatic diseases. ANAs may also be involved in the pathogenesis of cancer as well as other premalignant diseases (44). Meanwhile, ANA testing has come into common use in clinical practice. Growing evidence indicates that autoantibodies occur several years earlier than symptomatic AIDs. Because of this, clinicians are cautious when administering immunotherapy to these patients. Nevertheless, the prevalence of ANAs in the US has increased from 11.0% to 15.9% in the recent 2 decades (45). Therefore, there is an urgent need to clarify the effects of ANAs on the efficacy and safety of immunotherapy in tumor patients.

Our study analyzed a total of 159 Chinese patients diagnosed with locally-advanced or metastatic NSCLC and given immunotherapy (PD-1 or PD-L1 or CTLA-4 inhibition with or without chemotherapy). All patients were

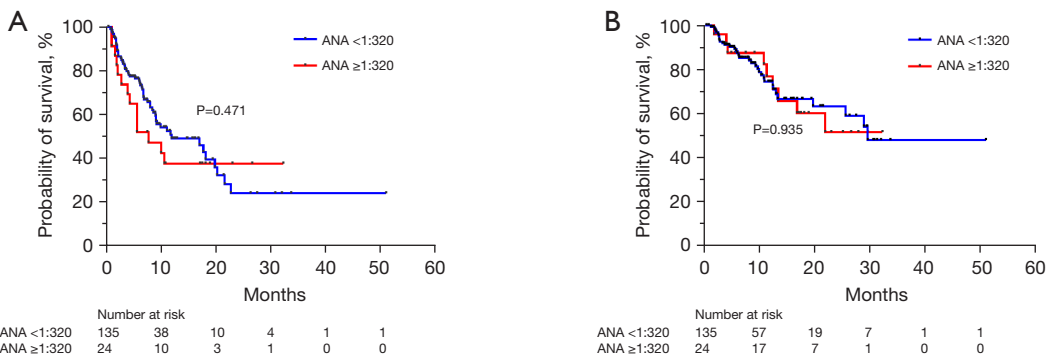




**Figure 3** Kaplan-Meier analysis of PFS (A) and OS (B) for patients with ANA titer <1:80 or ≥1:80. The P values were calculated with the log rank test. PFS, progression-free survival; OS, overall survival; ANA, antinuclear antibody.



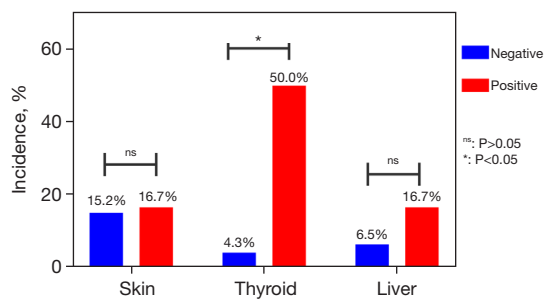
**Figure 4** Kaplan-Meier analysis of PFS (A) and OS (B) for patients with ANA titer <1:160 or ≥1:160. The P values were calculated with the log rank test. PFS, progression-free survival; OS, overall survival; ANA, antinuclear antibody.



**Figure 5** Kaplan-Meier analysis of PFS (A) and OS (B) for patients with ANA titer <1:320 or ≥1:320. The P values were calculated with the log rank test. PFS, progression-free survival; OS, overall survival; ANA, antinuclear antibody.

tested for the status of ANAs. The influence of different cut-off values of ANA titers including 1:80, 1:160, and 1:320 on the safety and efficacy of immunotherapy were also discussed. When using 1:80 or 1:160 as the cut-off values of negative or positive ANA, irAEs of any grade,

ORR, DCR, mPFS and median overall survival (mOS) of ICIs between groups showed no significant difference. However, with the cut-off value of 1:320, the incidence rates of irAEs were 25.9% vs. 45.8% (P=0.047) for patients in the negative or positive group. In multivariate models,



**Figure 6** Incidence of irAEs of any grade between patients with positive or negative ATG or ATPO. IrAEs, immune-related adverse events; ATG, anti-thyroglobulin; ATPO, anti-thyroid peroxidase; ns, not significant.

ANA titer  $\geq 1:320$  was also associated with irAEs (OR =4.9, 95% CI: 1.45–16.52,  $P=0.01$ ). Nevertheless, the probability of grade 3–4 adverse reactions did not increase significantly in the positive group. Further analysis showed a significant difference in the incidence of adverse skin reactions between the 2 groups (9.7% vs. 32%,  $P=0.003$ ). The ORR, DCR and mPFS between the ANA negative (ANA  $<1:320$ ) and positive groups (ANA  $\geq 1:320$ ) showed no significant difference. Besides, our study suggested patients with ATG or ATPO were more likely to suffer from thyroid dysfunction when receiving immunotherapy.

Meanwhile, we retrieved 4 relevant articles by searching the keywords “Immunotherapy”, “Immune Checkpoint Inhibitors”, “Neoplasms” and “Antinuclear Antibodies” on PubMed (Figure 7 and Table 4). Morimoto *et al.* conducted a retrospective study of 77 patients with advanced NSCLC treated with ICIs and chemotherapy, focusing on the effects of preexisting ANAs on the safety and efficacy of immunotherapy (20). Using ANA=1:160 as a cut-off value, patients were divided into the negative group (ANA  $<1:160$ ) and positive group (ANA  $\geq 1:160$ ). The incidence of irAEs of any grade in patients with or without ANAs was 62.5% vs. 49.3% ( $P=0.71$ ). Whereas, the incidence of discontinuation of all treatment components due to severe adverse events was higher in the ANA-positive group (50% vs. 15.9%,  $P=0.042$ ). The ANA-positive group had a shorter PFS and OS than the ANA-negative group [hazard ratio (HR) =2.11, 95% CI: 0.88–5.07,  $P=0.093$ ; and HR =3.11, 95% CI: 1.14–8.49,  $P=0.027$ , respectively].

However, according to the research performed by Sakakida *et al.* (19) which used the same cut-off value, the incidence of irAEs of any grade in both groups did not show a significant difference despite the fact that patients with

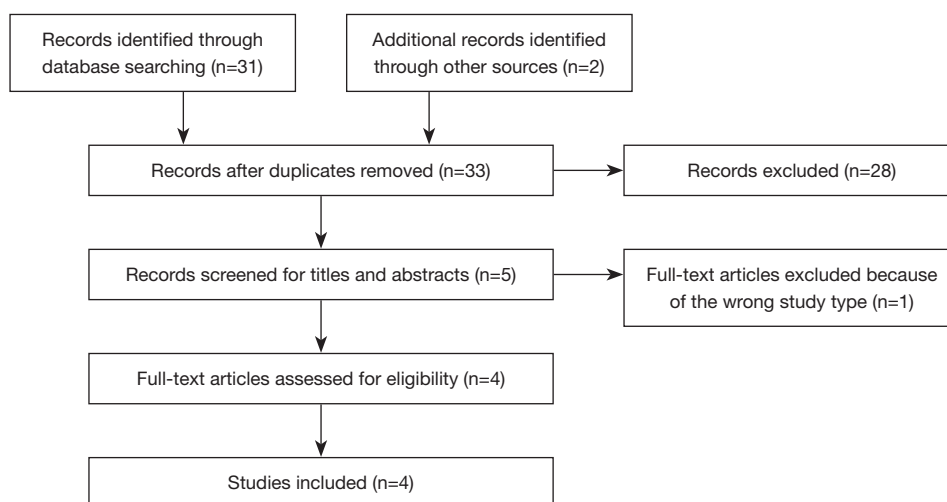
positive ANAs were more likely to develop colitis (2/9 vs. 3/182,  $P=0.0002$ ). Similarly, ORR and DCR also showed no significant differences between the 2 groups.

Moreover, using another cut-off value, some researchers obtained utterly different results. In 2019, Yoneshima *et al.* published an article using 1:40 as the cut-off value for negative or positive ANA (21). A total of 83 patients were analyzed in the study, and 18 (21.7%) were positive for ANA (ANA  $\geq 1:40$ ). Negative and positive groups did not differ in terms of the incidence of irAEs (32.3% vs. 33.3%), but PFS (3.8 vs. 2.9 months,  $P=0.03$ ) and OS (15.8 vs. 11.6 months,  $P=0.03$ ) were significantly longer in the negative group.

In another retrospective study involving 137 patients (15), the presence of preexisting antibodies including rheumatoid factor, ANAs, ATG, and ATPO was independently associated with any grade of irAEs (OR =3.25, 95% CI: 1.59–6.65,  $P=0.001$ ). The median PFS for patients with or without any preexisting antibodies was 6.5 months (95% CI: 4.4–12.9) vs. 3.5 months (95% CI: 2.4–4.1) (HR =0.53, 95% CI: 0.36–0.79,  $P=0.002$ ). However, in the subgroup analysis of patients with ANAs at pretreatment, there were no significant differences in the increase of the incidence of irAEs of any grade and benefits of PFS, ORR, DCR compared with those without ANAs.

It can be seen from the above studies that different research has shown quite different effects of preexisting ANAs on the safety and efficacy of immunotherapy. In terms of security (the incidence of irAEs), the negative group was not inferior to the positive group. However, in terms of efficacy (ORR or DCR or mPFS or mOS), several studies have drawn contrasting results. Our study suggested that with the cut-off value of 1:320, patients with preexisting ANAs were more likely to suffer from irAEs, especially in terms of skin adverse events. But no significant differences were observed regarding grade 3/4 irAEs. Besides, the status of ANAs might have no correlation with the clinical benefit of immunotherapy.

However, our study has some limitations. Firstly, its retrospective nature and limited number of patients, especially those with positive ANA (titer  $\geq 1:320$ ) or ATG/ATPO, may have introduced case selection bias and restricted the generalizability of the results. Moreover, the expression levels of PD-L1 were not routinely evaluated in China. Therefore, we were unable to assess the baseline expression levels of PD-L1 between groups. We believe further prospective investigations with a large sample size are urgently needed.



**Figure 7** Flow diagram for details on the study selection process.

**Table 4** Research on the influence of preexisting antinuclear antibodies on the safety and efficacy of immunotherapy in NSCLC patients

Author	Toi (15)	Yoneshima (21)	Sakakida (19)	Morimoto (20)
Year	2019	2019	2020	2020
Cases	137	83	191	77
Treatment	PD-1 monotherapy	PD-1 monotherapy	PD-1/PD-L1	ICI + chemotherapy
ANA cut-off value	1:40	1:40	1:160	1:160
Overall response rate (PG/NG)	38%/28%, P=0.35	NA	12.50%/26.50%, P=0.38	NA
Disease control rate (PG/NG)	77%/66%, P=0.26	NA	37.50%/67.50%, P=0.08	NA
Median progression-free survival (PG/NG) (months)	NA, P=0.67	2.9/3.8, P=0.03	NA	6.2/10.2, P=0.09
Median overall survival (PG/NG) (months)	NA	11.6/15.8, P=0.03	NA	7/not reached, P=0.02
Development of irAE (PG/NG)	60%/42%, P=0.05	33.30%/32.30%, P=1.00	44.40%/37.90%, P=0.69	62.50%/49.30%, P=0.71
Development of irAE $\geq$ grade 3 (PG/NG)	8%/6%, P=0.80	11.10%/6.20%, P=0.64	NA	37.50%/14.50%, P=0.13

NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; ICI, immune checkpoint inhibitor; ANA, antinuclear antibodies; PG, positive group, with preexisting ANAs; NG, negative group, without preexisting ANAs; NA, not applicable; irAE, immune-related adverse events.

## Conclusions

Our study suggested preexisting ANAs might not be associated with the clinical benefit of ICI treatment in patients with NSCLC. However, patients with ANA titer  $\geq$ 1:320 have a greater risk of suffering from skin adverse reactions. Additionally, patients with positive ATG or ATPO had the potential to develop abnormal thyroid function. In summary, for NSCLC patients with ANAs at baseline, we

believe that it may be acceptable to use immunotherapy under close monitoring for adverse reactions, especially for those with significantly elevated ANA titers. Further studies are still needed to confirm these findings.

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## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at <https://tclr.amegroups.com/article/view/10.21037/tclr-22-464/rc>

*Data Sharing Statement:* Available at <https://tclr.amegroups.com/article/view/10.21037/tclr-22-464/dss>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://tclr.amegroups.com/article/view/10.21037/tclr-22-464/coif>). LK receives honoraria from AMGEN. TH has received personal fees from Chugai Pharmaceutical outside the submitted work. MP received grants and consulting fees from BMS, MSD, Lilly, AZ and Takeda; received support for attending meetings from MSD and AZ; received payment honoraria for lectures from BMS, MSD, AZ and Takeda. 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 was performed in accordance with the principles for Good Clinical Practice and the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Peking Union Medical College Hospital on September 1, 2021 (No. S-K1744) and individual consent for this retrospective analysis was waived.

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