Translational Oncology 15 (2022) 101268

Contents lists available at ScienceDirect

Translational Oncology

journal homepage: www.elsevier.com/locate/tranon

Original Research

Factors associated with immunotherapy respond and survival in advanced non-small cell lung cancer patients

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ARTICLE INFO

Keywords:
Non-small cell lung cancer
Immune checkpoint inhibitors
Pre-treatment prognostic score
Immunotherapy respond
Immune-related adverse events

ABSTRACT

Objectives: This study aimed to explore factors associated with immunotherapy respond and survival in advanced non-small cell lung cancer (aNSCLC) patients treated with immune checkpoint inhibitors (ICIs).
Methods: A total of 101 patients with aNSCLC receiving ICIs were included. The association between clinical factors and multiple endpoints including objective response rate (ORR), disease control rate (DCR), overall survival (OS) and progression-free survival (PFS) were investigated by multivariate analyses.
Results: Multivariate logistic analyses revealed that clinical stage, lactate dehydrogena (LDH), and any grade immune-related adverse events (irAEs) were independent predictors of ORR, while LDH and ICIs treatment type were independent predictors of DCR. In Multivariate Cox analysis, Eastern Cooperative Oncology Group performance status (ECOG PS), LDH, albumin (Alb), platelet to lymphocyte ratio (PLR), and any grade irAEs were independent factors for OS. Similarly, clinical stage, LDH, Alb, and any grade irAEs were independent factors for PFS. Pre-treatment prognostic score was established based on clinical stage, ECOG PS, LDH, Alb and PLR to classify patients into three groups: the good group (0–1 score), the intermediate group (2 scores) and the poor group (3-4 scores). The immunotherapy response was significantly different in various prognostic groups. Subset analyses showed pre-treatment prognostic score $\geq$ 3 tended to have a strong negative impact on survival among patients with programmed cell death-ligand 1 (PD-L1) expression $\geq$ 50%.
Conclusions: Pre-treatment prognostic score based on clinical stage, ECOG PS, LDH, Alb and PLR may help to identify aNSCLC patients who may benefit from ICIs.

Introduction

Lung cancer is one of the leading causes of cancer-related death worldwide, accounting for nearly one-fifth of all cancer-related deaths [1]. Non-small cell lung cancer (NSCLC), which is comprised of approximately 85% of all lung cancer patients [1]. The vast majority of patients are already at an advanced stage when they are diagnosed, and the 5-year survival rate is only about 5% until the introduction of immuno-oncology (IO) treatments [2].

In recent years, immunotherapy has become an important tool in modern antitumor therapy. Immune checkpoint inhibitors (ICIs) have proven to significantly improve long-term survival in patients with advanced NSCLC [3–9]. However, not all patients respond to ICIs, and a minority of patients do not benefit from ICIs [10]. Currently, the more widely immunomarker used in the clinical setting is programmed cell death-ligand 1 (PD-L1) expression. Several studies have shown that PD-L1 expression levels are strongly correlated with the efficacy of immunotherapy [3,11,12]. However, the CheckMate-026 study found no significant benefit in PFS and OS for patients with high PD-L1 expression [13]. Although PD-Ll expression predicting the efficacy of immunotherapy is documented in the NCCN guidelines, it is not entirely accurate. In addition, tumor mutation burden (TMB) is another popular biomarker in recent years. But TMB test is expensive and technically complex, making it difficult to be applied universally in clinical practice. Therefore, it is necessary to discover more factors that affect the efficacy of immunotherapy and to select eligible patients who may benefit from ICIs.

A variety of evidence indicated that blood biomarkers such as LDH, Alb, neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), systemic inflammation index (SII), and systemic inflammation response index (SIRI) could facilitate the prediction of outcomes for various solid carcinomas [14–17]. These inflammatory biomarkers are

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https://doi.org/10.1016/j.tranon.2021.101268
Received 14 October 2021; Received in revised form 4 November 2021; Accepted 8 November 2021

simple and readily available in clinical practice. However, in currently, there are few studies combining hematological indicators to predict the prognosis of aNSCLC treated with ICIs. As such, we conducted a retrospective analysis to explore factors affecting treatment respond and survival in aNSCLC treated with ICIs, and establish a pre-treatment prognostic score that may help guide clinical treatment.

Patients and methods

Patients

We enrolled 101 patients who had treated with PD-1/PD-L1 inhibitors at Fujian Province Cancer Hospital. The inclusion criteria were: (1) diagnosed with aNSCLC; (2) received at least 1 cycle of ICIs. The exclusion criteria were: (1) had a second primary malignancy; (2) insufficient clinical or laboratory data. All patients were clinically staged using the American Joint Committee on Cancer (AJCC) 8th edition TNM staging system [18].

Data collections

The clinical information included age, sex, Eastern Cooperative Oncology Group performance status (ECOG PS), smoking, histology, clinical stage, brain metastases, bone metastases, liver metastases, PD-L1 expression, epidermal growth factor receptor (EGFR) mutation status, line of immunotherapy, thoracic radiotherapy, ICIs treatment type, immune-related adverse events (irAEs), and hematological markers including serum lactate dehydrogena (LDH) (U/L), albumin (Alb) (g/L), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), systemic inflammation index (SII), and systemic inflammation response index (SIRI).

The best cut-off values of serum markers

The NLR, PLR, SII, and SIRI were calculated as followed: NLR = absolute neutrophil count / absolute lymphocyte count, PLR = absolute platelet count / absolute lymphocyte count, SII=absolute neutrophil count × absolute platelet count / absolute lymphocyte count, and SIRI = absolute neutrophil count × absolute monocyte count / absolute lymphocyte count. All hematological markers were collected from one week before the initial of ICIs treatment. The best cut-off values for Alb, NLR, PLR, SII and SIRI were calculated using X-tile software (version 3.6.1), which is a valuable tool to generate the optimal cut-point with minimum p value. We used best cut-off values to divide patients into two groups: low NLR (≤3.1) versus high NLR (>3.1);low PLR (≤176) versus high PLR (>176); low SII (≤847) versus high SII (>847); low SIRI (≤1.6) versus high SIRI (>1.6); low Alb (≤35.4) versus high Alb (>35.4). The upper limit of normal (ULN) of LDH in our center was 250 U/L. Patients were divided into low LDH (≤250) and high LDH (>250).

Immune-related adverse events

Immune-related adverse events were categorized based on the organ/system: cutaneous irAEs, endocrine irAEs, gastrointestinal irAEs, hepatic irAEs, pulmonary irAEs, cardiac irAEs, and other irAEs. "Single site" irAEs referred to patients experiencing one of the categories of irAEs, while "Multiple sites" irAEs referred to experience different categories of irAEs [19]. All irAEs were graded by the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 5.0).

Endpoints

The overall survival (OS) was defined as the time between initial ICIs treatment and death for any reason or the last follow-up. The progression-free survival (PFS) was measured from the first time of ICIs treatment to the disease progression, death due to any cause, or time of last follow-up. The objective response rate (ORR) was defined as the proportion of patients who achieved a complete (CR) or partial response (PR). The disease control rate (DCA) was defined as the sum of CR, PR and stable disease (SD). Treatment response was assessed by Response Evaluation Criteria in Solid Tumors (RECIST).

Table 1
Characteristics of patients.

Parameter	Pooled Cohort (N = 101), N (%)
Age (years)	
<70	82(81.2)
≥70	19(18.8)
Sex	
Female	23(22.8)
Male	78(77.2)
Smoking history	
No	28(27.7)
Yes	73(72.3)
ECOG PS	
0	23(22.8)
1	74(73.3)
2	4(4.0)
Histology	
Squamous	35(34.7)
Nonsquamous	66(65.3)
Clinical stage	
IVA	33(32.7)
IVB	68(67.3)
Brain metastases	32(31.7)
Bone metastases	42(41.6)
Live metastases	12(11.9)
EGFR mutation status	
EGFR mutant	9(8.9)
EGFR wild type	61(60.4)
EGFR unknown	31(30.7)
PD-L1 expression	
<50%	20(19.8)
≥50%	23(22.8)
Unknown	58(57.4)
Line of immunotherapy	
First	33(32.7)
Second	44(43.6)
≥ Third	24(23.8)
Thoracic radiotherapy	26(25.7)
Immune treatment type	
ICI Monotherapy	25(24.8)
Combine with other therapy	76(75.2)
irAEs	
No	56(55.4)
Yes	45(44.6)
LDH (U/L)	
Low	68(67.3)
High	33(32.7)
Alb (g/L)	
Low	31(30.7)
High	70(69.3)
NLR	
Low	46(45.5)
High	55(54.5)
PLR	
Low	52(51.5)
High	49(48.5)
SII	
Low	49(48.5)
High	52(51.5)
SIRI	
Low	51(50.5)
High	50(49.5)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; ICIs, immune checkpoint inhibitors; PD-L1, programmed cell death-Ligand 1; EGFR, epidermal growth factor receptor; irAEs, immune-related adverse events; LDH, lactate dehydrogenase; Alb, albumin; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte; SII, systemic inflammation index; SIRI, systemic inflammation response index.

Table 2
Univariate and multivariate logistic analyses of factors associated with treatment response in aNSCLC patients treated with ICIs.

Variable	Objective respond rate Univariate analysis OR (95% CI)	*P* value	Multivariate analysis OR (95% CI)	*P* value	Disease control rate Univariate analysis OR (95% CI)	*P* value	Multivariate analysis OR (95% CI)	*P* value
Age (years)								
<70	1 (Reference)				1 (Reference)			
≥70	0.514(0.156–1.697)	0.275			0.796(0.281–2.256)	0.668		
Sex								
Female	1 (Reference)				1 (Reference)			
Male	1.417(0.499–4.020)	0.513			1.446(0.551–3.799)	0.454		
Smoking history								
No	1 (Reference)				1 (Reference)			
Yes	1.224(0.472–3.180)	0.677			1.857(0.752–4.586)	0.179		
ECOG PS								
0	1 (Reference)				1 (Reference)			
1	0.515(0.196–1.355)	0.179			0.911(0.331–2.510)	0.858		
2	0.433(0.039–4.818)	0.496			0.438(0.051–3.763)	0.451		
Histology								
Squamous	1 (Reference)				1 (Reference)			
Nonsquamous	0.833(0.348–1.996)	0.682			1.118(0.469–2.666)	0.801		
Clinical stage								
IVA	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
IVB	0.216(0.088–0.533)	0.001	0.218(0.079–0.601)	**0.003**	0.337(0.123–0.926)	0.035	0.599(0.158–2.276)	0.452
Brain metastases								
No	1 (Reference)				1 (Reference)			
Yes	0.625(0.244–1.602)	0.328			1.100(0.447–2.704)	0.836		
Bone metastases								
No	1 (Reference)				1 (Reference)		1 (Reference)	
Yes	0.427(0.173–1.054)	0.065			0.311(0.131–0.737)	0.008	0.572(0.177–1.840)	0.348
Live metastases								
No	1 (Reference)				1 (Reference)			
Yes	0.690(0.174–2.741)	0.598			0.643(0.188–2.202)	0.482		
EGFR mutation status								
EGFR mutant	1 (Reference)				1 (Reference)			
EGFR wild type	1.465(0.277–7.744)	0.653			1.768(0.427–7.331)	0.432		
EGFR unknown	2.211(0.392–12.465)	0.369			1.680(0.369–7.644)	0.502		
PD-L1 expression								
<50%	1 (Reference)				1 (Reference)			
≥50%	1.600(0.424–6.031)	0.488			0.667(0.187–2.377)	0.532		
Unknown	1.462(0.462–4.621)	0.518			0.952(0.315–2.879)	0.931		
Line of immunotherapy								
First	1 (Reference)				1 (Reference)			
Second	0.905(0.352–2.327)	0.836			0.804(0.297–2.173)	0.667		
≥ Third	0.461(0.137–1.550)	0.211			0.525(0.172–1.603)	0.258		
Thoracic radiotherapy								
No	1 (Reference)				1 (Reference)			
Yes	0.944(0.360–2.476)	0.907			1.875(0.671–5.236)	0.230		
Treatment type								
ICI monotherapy	1 (Reference)				1 (Reference)		1 (Reference)	
Combine with other therapy	1.020(0.387–2.689)	0.969			3.033(1.190–7.735)	0.020	2.925(1.046–8.177)	**0.041**
irAEs								
No	1 (Reference)		1 (Reference)		1 (Reference)			
Yes	2.933(1.232–6.987)	0.015	3.366(1.221–9.278)	**0.019**	2.000(0.841–4.754)	0.117		
LDH (U/L)								
Low	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
High	0.197(0.062–0.623)	0.006	0.185(0.051–0.671)	**0.010**	0.290(0.120–0.700)	0.006	0.341(0.131–0.883)	**0.027**
Alb (g/L)								
Low	1 (Reference)				1 (Reference)		1 (Reference)	
High	1.905(0.719–5.043)	0.195			2.708(1.118–6.563)	0.027	1.847(0.688–4.954)	0.223
NLR								
Low	1 (Reference)				1 (Reference)		1 (Reference)	
High	0.363(0.153–0.862)	0.022			0.461(0.171–1.238)	0.125	0.471(0.198–1.121)	0.089
PLR								
Low	1 (Reference)				1 (Reference)			
High	0.519(0.220–1.224)	0.134			0.483(0.207–1.128)	0.093		
SII								
Low	1 (Reference)				1 (Reference)			
High	0.435(0.184–1.029)	0.058			0.695(0.300–1.607)	0.394		
SIRI								
Low	1 (Reference)				1 (Reference)			
High	0.489(0.207–1.155)	0.103			0.617(0.267–1.429)	0.260		

Abbreviations: aNSCLC, advanced non-small cell lung cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; ICIs, immune checkpoint inhibitors; PD-L1, programmed cell death-Ligand 1; EGFR, epidermal growth factor receptor; irAEs, immune-related adverse events; LDH, lactate dehydrogenase; Alb, albumin; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte; SII, systemic inflammation index; SIRI, systemic inflammation response index; OR, odds ratio.

Table 3
Univariate and multivariate cox analyses of factors associated with OS and PFS in aNSCLC patients treated with ICIs.

Variable	Overall survival				Progression-free survival			
	Univariate analysis HR (95% CI)	*P* value	Multivariate analysis HR (95% CI)	*P* value	Univariate analysis HR (95% CI)	*P* value	Multivariate analysis HR (95% CI)	*P* value
Age (years)								
<70	1 (Reference)				1 (Reference)			
≥70	1.497(0.810–2.765)	0.198			1.264(0.716–2.234)	0.419		
Sex								
Female	1 (Reference)				1 (Reference)			
Male	0.793(0.441–1.426)	0.439			0.802(0.471–1.366)	0.416		
Smoking history								
No	1 (Reference)				1 (Reference)			
Yes	0.841(0.485–1.457)	0.537			0.851(0.513–1.411)	0.531		
ECOG PS								
0	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
1	1.729(0.896–3.338)	0.103	1.735(0.863–3.490)	0.122	1.394(0.774–2.511)	0.269	1.293(0.666–2.512)	0.448
2	4.443(1.221–16.169)	0.024	8.537(2.114–34.471)	**0.003**	3.232(1.051–9.944)	0.041	2.367(0.64–8.5707)	0.195
Histology								
Squamous	1 (Reference)				1 (Reference)			
Nonsquamous	0.931(0.561–1.546)	0.783			0.987(0.612–1.592)	0.959		
Clinical stage								
IVA	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
IVB	2.500(1.373–4.551)	0.003	1.731(0.809–3.705)	0.157	2.207(1.306–3.370)	0.003	2.182(1.181–4.030)	**0.013**
Brain metastases								
No	1 (Reference)				1 (Reference)			
Yes	1.524(0.903–2.570)	0.114			1.427(0.888–2.294)	0.142		
Bone metastases								
No	1 (Reference)		1 (Reference)		1 (Reference)			
Yes	1.665(1.006–2.754)	0.047	1.101(0.567–2.137)	0.777	1.441(0.914–2.272)	0.116		
Live metastases								
No	1 (Reference)				1 (Reference)			
Yes	1.085(0.485–2.427)	0.842			1.290(0.641–2.594)	0.476		
EGFR mutation status								
EGFR mutant	1 (Reference)				1 (Reference)			
EGFR wild type	0.664(0.278–1.583)	0.356			0.584(0.274–1.247)	0.165		
EGFR unknown	0.648(0.260–1.620)	0.354			0.564(0.250–1.274)	0.168		
PD-L1 expression								
<50%	1 (Reference)				1 (Reference)			
≥50%	0.951(0.457–1.979)	0.894			1.185(0.580–2.420)	0.642		
Unknown	0.940(0.494–1788)	0.851			1.177(0.632–2.190)	0.608		
Line of immunotherapy								
First	1 (Reference)				1 (Reference)			
Second	0.965(0.541–1.720)	0.904			1.042(0.607–1.790)	0.880		
≥ Third	1.035(0.527–2.033)	0.920			1.512(0.828–2.761)	0.178		
Thoracic radiotherapy								
No	1 (Reference)				1 (Reference)			
Yes	0.848(0.478–1.504)	0.573			0.944(0.565–1.577)	0.827		
Treatment type								
ICI monotherapy	1 (Reference)				1 (Reference)			
Combine with other therapy	0.847(0.478–1.502)	0.570			1.165(0.690–1.966)	0.568		
irAEs								
No	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Yes	0.557(0.328–0.946)	0.030	0.522(0.293–0.930)	**0.027**	0.592(0.352–0.997)	0.048	0.570(0.337–0.967)	**0.037**
LDH (U/L)								
Low	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
High	2.659(1.568–4.511)	<0.001	2.431(1.342–4.404)	**0.003**	2.135(1.321–3.450)	0.002	1.924(1.127–3.284)	**0.016**
Alb (g/L)								
Low	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
High	0.457(0.274–0.764)	0.003	0.499(0.273–0.913)	**0.024**	0.607(0.377–0.976)	0.039	0.593(0.353–0.997)	**0.049**
NLR								
Low	1 (Reference)		1 (Reference)		1 (Reference)			
High	2.086(1.240–3.510)	0.006	2.467(0.656–9.275)	0.181	1.390(0.879–2.198)	0.159		
PLR								
Low	1 (Reference)		1 (Reference)		1 (Reference)			
High	1.963(1.180–3.264)	0.009	2.069(0.999–4.287)	**0.050**	1.347(0.855–2.119)	0.200		
SII								
Low	1 (Reference)		1 (Reference)		1 (Reference)			
High	1.832(1.099–3.054)	0.020	0.408(0.105–1.590)	0.196	1.185(0.753–1.867)	0.461		
SIRI								
Low	1 (Reference)		1 (Reference)		1 (Reference)			
High	1.753(1.059–2.904)	0.029	0.764(0.319–1.828)	0.545	1.372(0.867–2.173)	0.177		

Abbreviations: aNSCLC, advanced non-small cell lung cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; ICIs, immune checkpoint inhibitors; PD-L1, programmed cell death-Ligand 1; EGFR, epidermal growth factor receptor; irAEs, immune-related adverse events; LDH, lactate dehydrogenase; Alb, albumin; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte; SII, systemic inflammation index; SIRI, systemic inflammation response index; HR, hazard ratio.

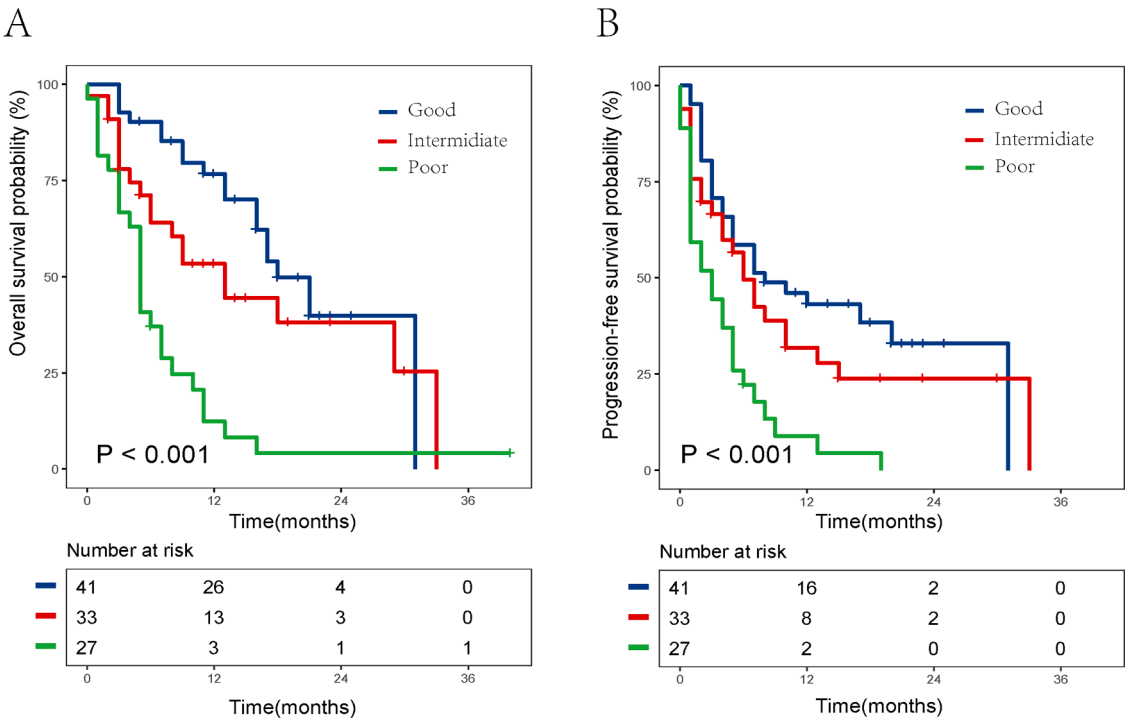

Fig. 1. Overall survival (A) and progress-free survival (B) according to pre-treatment prognostic score in advanced non-small cell lung cancer.

Statistical analyses

We compared categorical variables by Chi-squared test or Fisher exact test. The Kaplan-Meier method was used to plot survival curves, and the differences between survival curves were compared by the log-rank test. Multivariate logistic regression analysis was performed to find factors related to treatment respond. Variables with a *P*-value ≤0.05 in the univariate analysis were included in the Multivariate Cox analysis. Multivariate Cox hazards regression analysis was used to identify independent prognostic factors associated with survival. Pre-treatment prognostic score was established based on these factors to categorize patients in three groups (good, 0-1 score; intermediate, 2 scores; poor, ≥ 3 scores). The time-dependent receiver operating characteristic (ROC) curve was used to assess the prediction performance of pre-treatment prognostic score. All analyses were considered as statistically significant with a two-sided P-value of ≤0.05, and were performed using SPSS 24.0 (IBM, Armonk, NY, USA).

Results

The characteristics of patients

A total of 101 aNSCLC patients treated with ICIs were included in our study. The characteristics of patients were given in Table 1. Of the 101 patients, 78 (77.2%) were males, 19 (18.8%) were ≥70 years, 66 (65.3%) had nonsquamous, 73 (72.3%) had a history of smoking, 68 (67.3%) were clinical stage IVB, 97 (96.0%) had ECOG PS 0-1, 9 patients (8.9%) had EGFR mutations, and 23(22.8%) had PD-L1 expression ≥50%. At the time of ICIs start, brain / bone / liver metastases were present in 31.7%, 41.6%, 11.9% of patients. Furthermore, patients received ICIs as first-line treatment in 44 (43.6%), second-line in 33 (32.7%), and third or further-line in 24 (23.9%).

Factors associated with treatment response in aNSCLC patients treated with ICIs

For the entire cohort, there were 32 (31.7%) patients with PR, 36 (35.6%) with SD, and 33 (32.7%) with PD. None of the patients had CR. The overall ORR and DCR were 31.7% and 67.3% respectively. In the multivariate logistic regression analyses, clinical stage (HR, 0.218; 95% CI, 0.079 to 0.601; $P = 0.003$), LDH (HR, 0.185; 95% CI, 0.051 to 0.671; $P = 0.010$), and any grade irAEs (HR, 3.366; 95% CI, 1.221 to 9.278; $P = 0.019$) were independent predictors of ORR, while LDH (HR, 0.341; 95% CI, 0.131 to 0.883; $P = 0.027$) and ICI treatment type (HR, 2.925; 95% CI, 1.046 to 8.177; $P = 0.041$) were independent predictors of DCR (Table 2).

Factors associated with OS and PFS in aNSCLC patients treated with ICIs

Univariate and Multivariate cox analysis for OS and PFS were detailed in Table 3, respectively. In Univariate cox analysis, the factors significantly correlated with worse OS were clinical stage IVB ($P = 0.003$), ECOG PS 2 ($P = 0.024$), bone metastases ($P = 0.047$), high LDH ($P < 0.001$), low Alb ($P = 0.003$), high NLR ($P = 0.006$), high PLR ($P = 0.009$), high SII ($P = 0.020$), and high SIRI ($P = 0.029$). Also, any grade irAEs had a positive impact on OS ($P = 0.030$). In Multivariate Cox analysis, only ECOG PS 2 (HR: 6.214, 95%CI: 1.438 to 26.859, $P = 0.014$), high LDH (HR: 2.431, 95%CI: 1.342 to 4.404, $P = 0.003$) were associated with decreased OS. By comparison, high Alb (HR: 0.499, 95% CI: 0.273 to 0.913, $P = 0.024$) and any grade irAEs (HR: 0.522, 95%CI: 0.293 to 0.930, $P = 0.027$) were associated with increased OS. Similarly, In Multivariate cox analysis for PFS indicated that clinical stage IVB (HR: 2.182, 95%CI: 1.181 to 4.030, $P = 0.013$), and high LDH (HR: 1.924, 95%CI: 1.127 to 3.284, $P = 0.016$) were independent negative factors while high Alb (HR: 0.353, 95%CI: 0.353 to 0.997, $P = 0.049$) and any grade irAEs (HR: 0.570, 95%CI: 0.337 to 0.967, $P = 0.037$) were independent favorable factors.

The development and evaluation of pre-treatment prognostic score

The clinical stage, ECOG PS, LDH, PLR, and Alb were considered as significant prognostic factors for survival. Patients with clinical stage IVB, ECOG PS 2, high LDH, high PLR, or low Alb were regarded as 1 score. Based on these prognostic factors, we then classified patients into

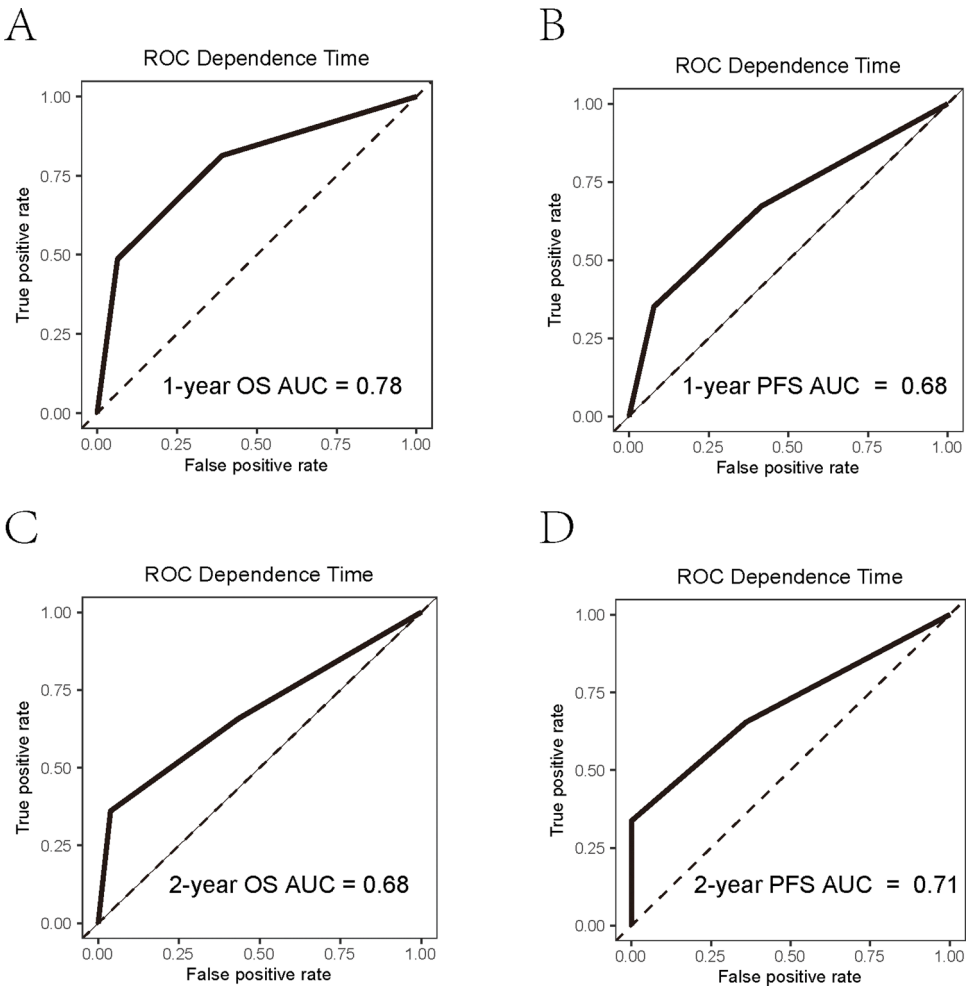

Fig. 2. Time-dependent receiver operating characteristic (ROC) for pre-treatment score for predicting 1-year overall survival (A), 1-year progress-free survival (B), 2-year overall survival (C), and 2-year progress-free survival (D).

Table 4
Response to immunotherapy based on pre-treatment prognostic score.

	All (n = 101)	Good (n = 41)	Intermediate (n = 33)	Poor (n = 27)	P value
Best overall response-no. (%)					**0.016**
CR	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
PR	32 (31.7)	19 (46.3)	9 (27.3)	4 (14.8)	
SD	36 (35.6)	14 (34.1)	14 (42.4)	8 (29.6)	
PD	33 (32.7)	18 (19.5)	10 (30.3)	15 (55.6)	
Objective response rate-no. (%)	32 (31.7)	19 (46.3)	9 (27.3)	4 (14.8)	**0.020**
Disease control rate-no. (%)	68 (67.3)	33 (80.5)	23(69.7)	12 (44.4)	**0.009**

Abbreviations: ORR, objective response rate; DCR, disease control rate; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

3 categories. 41 patients were assigned to the good group (0-1 score), 33 to the intermediate group (2 scores) and the remaining 27 patients to the poor group (≥3 scores). Kaplan-Meier analysis showed that median OS were 18, 13 and 5 months in the good group, the intermediate group and the poor group, respectively ($P < 0.001$) (Fig. 1A), and median PFS of three prognostic groups were 8, 6 and 3 months, respectively ($P < 0.001$) (Fig. 1B).

The time dependent AUC values of the ROC curves for the prediction of OS and PFS according to pre-treatment prognostic score were shown in Fig. 2. The time dependent AUC values for the prediction of 1- year OS, 2- year OS, 1- year PFS and 2- year PFS were 0.78, 0.68, 0.68 and 0.71, respectively (Fig. 2).

Table 5
Subgroup analyses of the relationship between survival and pre-treatment prognostic score according to PD-L1 expression.

	Overall survival HR (95% CI)	P value	Progression-free survival HR (95% CI)	P value
PD-L1 TPS <50%				
Good (0-1 score)	1 (Reference)		1 (Reference)	
Intermediate (2 scores)	2.317 (0.606–8.856)	0.219	1.183 (0.353–3.962)	0.785
Poor (≥ 3 scores)	5.329 (0.753–37.726)	0.094	1.635 (0.284–9.394)	0.582
PD-L1 TPS ≥50%				
Good (0-1 score)	1 (Reference)		1 (Reference)	
Intermediate (2 scores)	0.767 (0.079–7.436)	0.819	1.903 (0.383–9.451)	0.432
Poor (≥ 3 scores)	4.934 (1.317–18.491)	**0.018**	4.023 (1.119–14.461)	**0.033**

Table 6.
Summary of immune-related adverse events.

	Pooled Cohort ($N = 101$), N (%)
All grade irAEs (any)	45 (44.6)
Cutaneous	6 (5.9)
Endocrine	13 (12.9)
Gastrointestinal	4 (4.0)
Hepatic	9 (8.9)
Pulmonary	23 (22.8)
Cardiac	1 (1.0)
Others	3 (3.0)
1-2 grade irAEs (any)	37 (36.6)
Cutaneous	5 (5.0)
Endocrine	12 (11.9)
Gastrointestinal	2 (2.0)
Hepatic	6 (5.9)
Pulmonary	17 (16.8)
Cardiac	0 (0.0)
Others	3 (3.0)
≥3 grade irAEs (any)	8 (7.9)
Cutaneous	1 (0.0)
Endocrine	1 (0.0)
Gastrointestinal	2 (1.0)
Hepatic	3 (1.0)
Pulmonary	6 (5.9)
Cardiac	1 (0.0)
Others	0 (0.0)
Type of irAEs	
Single site	33 (32.7)
Multiple sites	12 (11.9)
Time to onset irAEs	
≤2 months	29 (28.7)
>2 months	16 (15.8)

The association between pre-treatment prognostic score and treatment response

According to pre-treatment prognostic score, the ORR for patients with 0-1, 2, ≥3 scores were 46.3%, 27.3%, and 14.8%, respectively, and the DCR for patients with 0-1, 2, ≥3 scores were 80.5%, 69.7%, and 44.4%, respectively (Table 4). The immunotherapy response was significantly different in various prognostic groups. Patients with a low prognostic score having a higher ORR and DCR ($P < 0.05$).

Subgroup analyses of the relationship between pre-treatment prognostic score and outcome according to PD-L1 expression

We conducted subgroup analyses of the relationship between pre-treatment prognostic score and outcome according to PD-L1 expression. Pre-treatment prognostic score ≥ 3 scores tended to have strong negative impact on OS (HR: 4.934, 95%CI: 1.317 to 18.491, $P = 0.018$) and PFS (HR: 4.023, 95%CI: 1.119 to 14.461, $P = 0.033$) among patients with PD-L1 TPS ≥ 50% (Table 5).

Immune-related adverse events and survival

All irAEs are summarized in Table 6. A number of 45 (44.6%) patients experienced any grade irAEs, 37 (36.6%) patients experienced 1/2 grade irAEs, and 8 (7.9%) patients experienced ≥ 3 grade irAEs. The most common irAEs involved the pulmonary, followed by the endocrine system and hepatic. The median OS and PFS in patients who experienced any grade irAEs was significantly higher than patients who did not experience irAEs (the median OS: 17 and 9 months, respectively, $P = 0.024$ (Fig. 3A); the median PFS: 7 and 4 months, respectively, $P = 0.026$ (Fig. 4A)). Furthermore, patients who experienced irAEs with grade 1/2, single-site, onset time less than 2 months had better survival than patients who experienced other categories of irAEs or did not experience irAEs (Figs. 3 and 4).

Discussion

With the development of immunology, immunotherapy has gradually become a current research hotspot. However, these are not sufficient to accurately predict immune response [20,21]. Therefore, it is necessary to identify more factors affecting the efficacy of immunotherapy. This study aims to explore potential predictors of immunotherapy efficacy in the real world by retrospectively analyzing clinical characteristics, and hematological markers in aNSCLC patients treated with ICIs.

First, we found that the nutritional status of patients significantly affected the efficacy of immunotherapy. Serum albumin level is an indicator of the nutritional status of patients. Our results showed that high Alb before immunotherapy had better survival. Similarly, high Alb also has a better prognosis for NSCLC treated with other anti-cancer therapies [22]. Takada et al. revealed that serum Alb level was an important prognostic marker for anti-PD-1 therapy in NSCLC patients. They found that Alb ≥3.5 g/dL was an independent predictor of DCR, PFS, and OS [16]. Lin et al. also found an association with poorer OS in patients with low Alb [23]. Poor nutritional status affects the efficacy of ICI on the one hand, probably because the high catabolic activity in malnutrition reactions may lead to an accelerated clearance of monoclonal antibodies [24]. On the other hand, chronic inflammation associated with malnutrition may suppress the activation of the immune system [25].

Second, we found that ECOG PS is an important prognostic factor affecting patients with aNSCLC receiving ICIs. In further, better baseline ECOG PS was also associated with better clinical outcomes in patients with aNSCLC receiving other anti-cancer drugs such as chemotherapeutic or targeted agents [26,27]. ECOG PS is commonly used to assess the general status of patients. Many previous retrospective studies have shown that ECOG PS ≥2 is associated with poor prognosis in NSCLC treated with ICIs [28–31]. Prelaj et al. considered ECOG PS 2 (HR 1.79, $p < 0.001$) as an independent negative prognostic factor [31]. Greil et al. similarly found that baseline ECOG performance status correlated with survival in patients with aNSCLC treated with ICIs. Their findings showed that patients with ECOG ≤ 1 had better OS compared to those with ECOG > 1 [28]. Similar to their results, in our multivariate Cox analysis, we found that ECOG PS 2 was associated with worse OS. Patients with poorer ECOG PS usually mean that the body has a weaker immune system and poorer lymphocyte function. Therefore, these patients may not be able to activate their immune system to fight the tumor and affect the efficacy of immunotherapy.

In addition, we found that LDH is an important biomarker that has significant value in determining immunotherapy response and prognosis. Our results show that LDH is not only significantly associated with immunotherapy response, but also affects patient survival prognosis. Studies have shown that serum LDH levels are closely related to hypoxic state, neovascularization, metastasis and poor prognosis of malignant tumors [32]. Elevated LDH facilitates malignant metastasis and cancer cell antagonism to hypoxia-induced apoptosis [33]. Similar to our findings, Adachi et al. concluded that pre-treatment LDH elevation was significantly correlated with poorer PFS and OS in NSCLC patients after ICIs treatment [34]. In addition, a large multicenter study also suggested that baseline LDH levels are an important prognostic biomarker for aNSCLC [35]. However, the mechanisms of how LDH affects the efficacy of immunotherapy are less studied, and more research is needed to elucidate the underlying mechanisms in the future.

We also found that high PLR was associated with poorer prognosis. However, the underlying mechanisms are not clear. Some studies mentioned that platelets can exert pro-tumor activity by stimulating cancer cell proliferation as well as promoting metastasis of tumor. Whereas lymphocytes mediate immune system function, and a decrease in lymphocytes indicates impaired cell-mediated immune function [36,37]. The relationship between PLR and the prognosis of patients receiving ICIs has been explored in the past [15,38,39]. They consensus that patients with high PLR have better prognosis and are more likely to

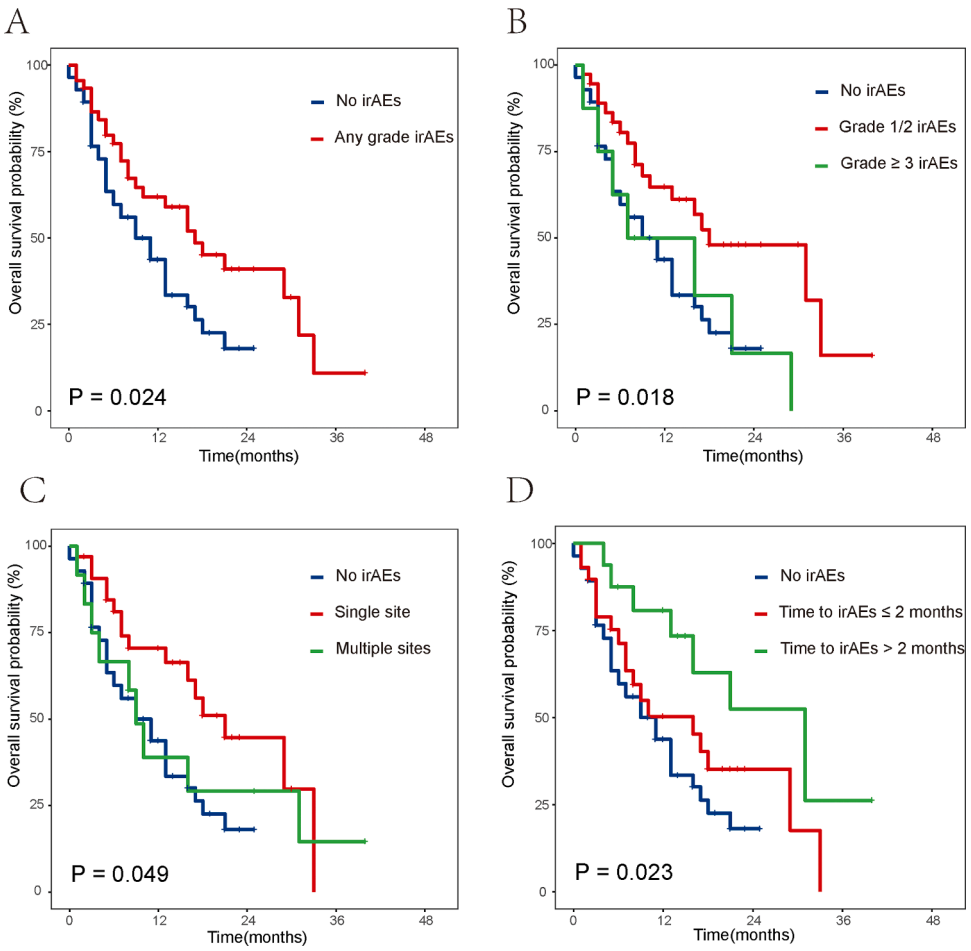

Fig. 3. Kaplan-Meier curves for overall survival according to any grade irAEs occurrence (A), 1/2 or ≥ 3 grade irAEs occurrence (B), single or multiple-site irAEs occurrence (C), and time to irAEs occurrence (D).

benefit from immunotherapy compared to patients with low PLR.

In addition to this, our study also proposed that patients with clinical stage IVA had better PFS and ORR compared to patients with clinical stage IVB. Finally, we combined clinical stage, ECOG PS, LDH, Alb and PLR to establish a novel pre-immunotherapy prognostic score, which divided patients into three groups: the good, the intermediate and the poor group, with statistical differences in immunotherapy response and survival between different groups. The time-dependent AUC values for predicting 1-year OS, 2-year OS, 1-year PFS, and 2-year PFS were 0.78, 0.68, 0.68, and 0.71, respectively, according to the pre-treatment prognostic score, indicating that the scoring system has good predictive ability. In addition, we performed a subgroup analysis of the relationship between pretreatment prognostic score and prognosis according to PD-L1 expression. In patients with PD-L1 TPS ≥50%, pre-treatment prognostic score ≥3 score had a strong negative effect on OS and PFS.

Finally, we also found that the occurrence of irAEs was significantly associated with survival. In our study, 44 patients (44.6%) experienced any grade irAEs, most patients (36/44) experienced grade 1/2 irAEs, and only a small proportion of patients (8/44) experienced grade ≥3 irAEs. The findings showed that the occurrence of irAEs was significantly associated with longer OS, PFS. In addition, patients who experienced irAEs with grade 1/2, single-site, onset time less than 2 months had better survival than those who experienced other categories of irAEs or did not experience irAEs. This result suggests that the occurrence of minor immune adverse events during ICIs treatment implies that patients may have a better prognosis. Several previous studies have demonstrated a significant association between irAEs with improved outcomes with. A large real-life cohort of 877 NSCLC patients showed a correlation between the occurrence of irAEs and survival. They reported that the occurrence of irAEs improved prognosis, but grade 3/4 irAEs did not prolong PFS or OS [19]. A multicenter study that included 531 patients with metastatic NSCLC also confirmed that patients with irAEs apparently had better PFS and OS [29]. Thus, irAEs may be one of the useful predictors for identifying patients who are likely to perform well on ICIs therapy.

There are several limitations of our current study. First, this is a retrospective study, so there may be selective bias in our study and a large prospective study is needed to validate our findings. Second, the number of patients meeting the inclusion criteria was small and all patients were from one institution. Therefore, larger sample studies are needed to further confirm the reliability of our results. Third, our current study only explored parameters that are commonly used and easily accessible in clinical practice, but other relevant variables involving genomics and radiomics may provide more valuable information to improve the predictive accuracy.

Conclusion

Pre-treatment prognostic score based on clinical stage, ECOG PS, LDH, Alb and PLR may help to identify aNSCLC patients who may benefit from ICIs. Among patients with PD-L1 expression ≥ 50%, pre-treatment prognostic score ≥ 3 tended to have a strong negative impact on survival. In addition, irAEs may be one of the useful predictors for identifying patients who are likely to perform well on ICIs therapy. Prospective randomiezd trials with larger numbers of patients were

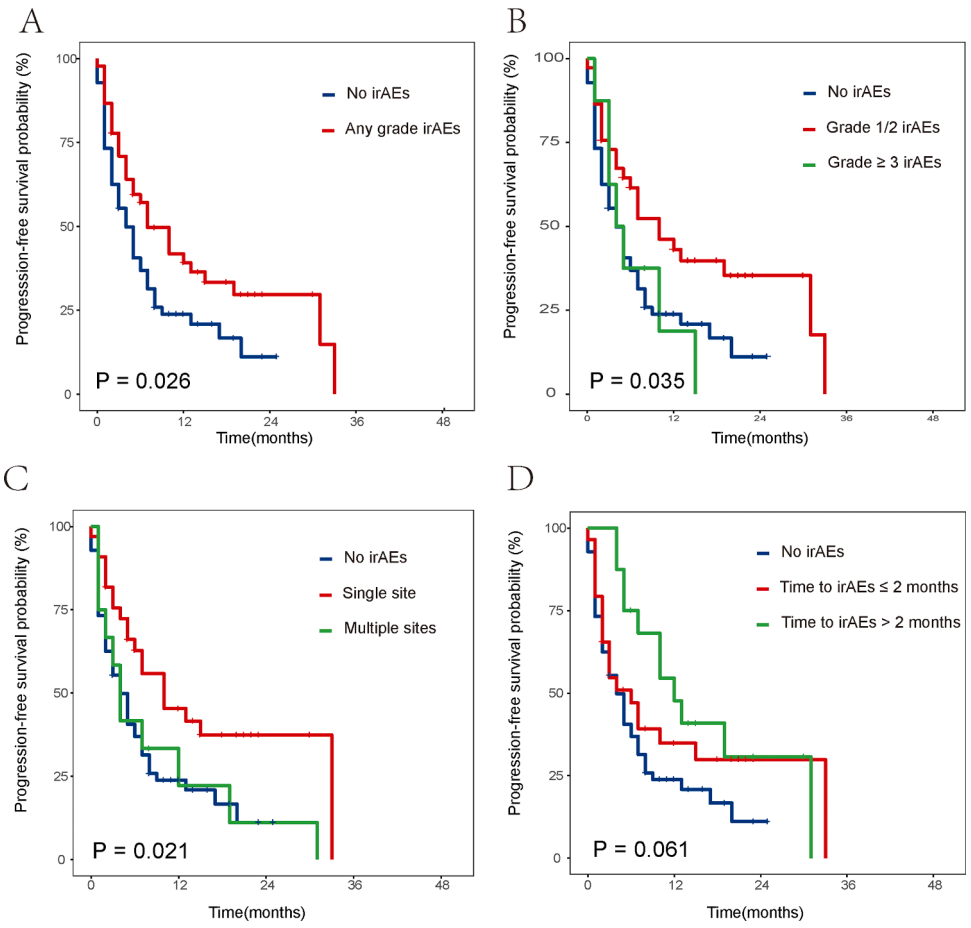

Fig. 4. Kaplan-Meier curves for progression-free survival according to any grade irAEs occurrence (A), 1/2 or ≥ 3 grade irAEs occurrence (B), single or multiple-site irAEs occurrence (C), and time to irAEs occurrence (D).

needed to performed to validate our results.

Ethics approval

This study was approved by the ethics committee of the Fujian Province Cancer Hospital and conducted in accordance with the principles of the Declaration of Helsinki and its amendment. All the patients signed informed consent. The authors are accountable for all aspects of the work and for ensuring that questions related to the accuracy or integrity of all parts of the work are appropriately investigated and resolved.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Disclosure

The authors report no conflicts of interest in this work.

Funding

This study was supported in part by grants from Wu Jieping Foundation (Grant number: 320.6750.19053).

CRediT authorship contribution statement

Yahua Wu: Data curation, Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. **Haishan Wu:** Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. **Mingqiang Lin:** Writing – review & editing. **Tianxiu Liu:** Writing – review & editing. **Jiancheng Li:** Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing.

CRediT authorship contribution statement

Yahua Wu: Data curation, Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. **Haishan Wu:** Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. **Mingqiang Lin:** Writing – review & editing. **Tianxiu Liu:** Writing – review & editing. **Jiancheng Li:** Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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